# Surgery for Snoring and Obstructive Sleep Apnea Syndrome

edited by Mario Fabiani

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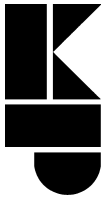
*ROMA OSAS – Conferences on the Diagnosis and Therapy of Snoring and OSAS were held in Rome on September 23rd-27th, 1997, March 1st-4th 2000, and March 6th-9th, 2002. Some of the abstracts presented at these Conferences are published in this book.*

*To my dearest Alma,*
*Valerio, Claudia and Antonio,*
*who switch on the beams of their love*
*in my dark moments*

# SURGERY FOR SNORING AND OBSTRUCTIVE SLEEP APNEA SYNDROME

Diagnosis and Therapy of Sleep Respiratory Disorders for the Otorhinolaryngologist

edited by Mario Fabiani



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# FOREWORD

*'Bocca della Verità' or 'Mouth of Truth' is the logo of the Unit for the Study and Therapy of Sleep Respiratory Disorders at the University of Rome 'La Sapienza'. It was chosen because its round shape with surprised expression, small nose and open mouth mirrors the typical face of a patient with OSAS (pre-therapy). The stone (diameter 1.75 m) in fact represents the face of a screaming faun and was originally found in the Mercury Temple area. According to popular legend, anyone putting his hand in the mouth will have it cut off if he has told a lie.*

When I first became involved in the field of OSAS about ten years ago, I had no idea that this activity would become foremost in both my professional and my academic life.

My curiosity was aroused when a patient of mine, an extremely fat patient, whom I had been following for a long time regarding a hearing problem, asked me for a prescription for CPAP. He had read in a newspaper that this device could solve his nocturnal respiration and diurnal hypersomnolence problems. Suddenly, I was confronted with documentation on snoring, OSAS, polysomnography, upper airway surgery, and positive pressure devices.

I was then, and still am now, a Professor of Audiology. Audiology was and still is the object of my love, but it is mainly a speculative discipline. It involves physics, electronics, psychology, rehabilitation, and great possibilities for basic research. However, only rarely does an audiological patient obtain full satisfaction clinically. Patients with neurosensorially-based deafness can be rehabilitated, but with difficulty; conductive hearing loss is light and recovers automatically in most cases; in a few cases, the patient can be packed up and delivered to the ear surgeon or audioprosthetic technician.

Vertigo is dramatic, but recovers spontaneously or after long-term rehabilitation, or it is categorized as a neurological symptom. Tinnitus is frustrating and the audiologist centers most of his time and energy on trying to convince the patient to forget it. In fact, it is very rare to see a patient affected by an audiological disease recover after intervention by an audiologist. Furthermore, most patients are either very old or very young.

With OSAS patients, things are very different. The patient is usually at the peak of his life; he has serious disturbances in his social, familial, and working spheres; he is sedentary and is often a manager with a disordered of lifestyle (does not partake in any sport; smokes and drinks too much), he has become irritable, apathetic, and is starting to worry about dying during the night or suffocating. He has been followed for years for his arterial hypertension and

latent arrhythmia. He, or often she, is a snorer and, after complaints from their partner, sleeps in a separate room. His sex life is affected, and he often gets up during the night convinced that he has prostatic problems too.

Unfortunately, for many years, no-one thought that these kinds of patients should consider consulting an otolaryngologist, and, at the same time, otolaryngologists never thought of taking care of this pathology.

As soon I started to see the first cases and was able to solve their obstruction, the number of patients being referred grew dramatically, as did my skill in this field. It was a really rewarding job. After years of hyperspecialistic practice, I returned to patient care in its entirety. Sometimes, a simple intervention such as nasal septoplasy or tonsillectomy, *i.e.*, one of those interventions so often underestimated by more expert colleagues, was able to solve some of the serious problems of life. In the meantime, specific new techniques came into being: radiofrequencies, oral appliances, diode lasers, tongue suspension devices, while, at the same time, diagnostic instrumentation such as polysomnography became more flexible and could more easy to be applied to obstructive disorders.

By 1997, my department was in an uproar about OSAS since I had got most of my colleagues interested in becoming involved, and the first sponsor was my former chief, Roberto Filipo, who gave me his approval, space to work in, and encouragement to overcome all the problems. My other colleagues, and I would like to mention all of them here: Giorgio Bandiera, Maurizio Barbara, Gian Antonio Bertoli, Ferdinando D'Ambrosio, Elio De Seta, Simonetta Masieri, Antonio Minni, Simonetta Monini, Virgilio Pizzichetta, Mario Patrizi, Maurizio Saponara, and Antonino Sciuto, either directly or indirectly, also offered to put their experience into writing various sections for this book. A specific section was also organized at the Institute, and I was able to coordinate some of our residents who have recently taken on the task of apostles, spreading the knowledge they acquired on OSAS during their time with us to other hospitals in the region. I must mention them too, since very often they did most of the work, and in OSAS, that is a lot of work: Francesca Auriti, Angelo Clarici, Fulvio Di Fulvio, Arianna Mattioni, Angela Mollica, Maria Laura Panatta, Barbara Pichi, Raniero Pucci, Mario Rinaldi, Rocco Roma, Anna Sambito, Ilenia Schettino, Rocco Schettino, Emanuela Sitzia, Artur Zajmi, and others.

The diagnosis and treatment of, and scientific research into, OSAS is a multidisciplinary task, and I succeeded in involving many professors from related disciplines at the hospital of the University 'La Sapienza': Carlo Cannella for Alimentation and Human Nutrition, Eugenio Gaudio for Anatomy, Giuseppe Calcagnini for Cardiology, Vincenzo Bonifacio and Debora Giannini for Endocrinology, Adolfo Francesco Attili for Gastroenterology, Franco Angelico for Internal Medicine, Giorgio Iannetti for Maxillo-Facial Surgery, Giuseppe Amabile for Neurology, Maria Pia Villa for Pediatrics, Alessandro Perrone and Ilio Cammarella for Pneumology, and Carlo De Dominicis for Urology. They used their experience in treating these patients and present their results in their contributions to this book.

During the same period, the diagnosis and therapy of OSAS was spreading fast to all otolaryngological units at universities and hospitals throughout Italy. It was easy for me to share my enthusiasm, and thus we built up a network of close cooperation. Any otolaryngologist will know these contributors so well that it would be easy for him to find their papers in this book, but still I want to mention those who were closest in advising and helping me: Marco Fusetti from L'Aquila, Luigi D'Angelo and Vieri Galli from Naples, Pietro Ferrara, Riccardo Speciale and Salvatore Restivo from Palermo, Oskar Schindler from Turin, and Maurizio Maurizi and Vittorio Pierro from Rome.

The time was now ripe to confront the world nomenclature on OSAS. The dream to share a rendezvous with all (or most of) the prominent people from all the disciplines involved in both the clinical and scientific research on OSAS was realized in 1997 at the 'ROMA OSAS – First International Conference on the Diagnosis and Therapy of Snoring and OSAS', which was followed by a second meeting in the year 2000, and a third in 2002. I only have to mention the names of the presidents of these conferences to testify to the high quality that was achieved: Giovanni Bonsignore, Gisle Djupesland, Roberto Filipo, Christian Guilleminault, Meir Kryger, Elio Lugaresi. It would be inappropriate to mention here only some of those who also took part, and there are too many to mention them all, since they are all equally important. I was very honored to ask them for and to receive papers for this book. Some of the abstracts presented at these conferences are also included in this book as highlights on various subjects, due to their particular relevance.

And so, finally, you now know how this book was born. It is the collection of an enthusiastic beginner who persuaded his friends and/or colleagues from his department, his university, his country, and the entire scientific community, to submit papers on the basics and state-of-the-art of relevant topics regarding snoring and OSAS, which, hopefully, in its turn will help those other enthusiastic beginners who wish to improve their knowledge on the care of apneic patients.

Also, even though many of the chapters are written by participants at the ROMA OSAS Conferences, this book is not an abstract volume of those meetings. It does, however, represent the scientific development unearthed on those occasions. For this reason, I think it would also be a valid textbook on OSAS from an otolaryngological point of view.

After the many thanks due to the contributors, my final thanks must go to the person who had the patience to cooperate with me on the editorial work: Peter Bakker of Kugler Publications. My confrontations with him were often thorny, but we both had the same goal in mind: to offer you the best possible product. We hope that you will agree with us that this book will be a useful addition, both to your practice and to your continuing education.

Mario Fabiani

# BASICS

# ANATOMO-PHYSIOLOGY OF THE UPPER AIRWAYS

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It is well known that the act of breathing, apparently so simple and natural, presupposes the existence of fine mechanisms of vascular regulation, and the presence of a normal morphology of the respiratory system, especially of the upper airways.

During a lifetime of breathing, the delicate tissues of the entire respiratory system are constantly exposed to environmental pollutants, to many living organisms, and to toxic chemicals. This constant situation has been the determining factor in the development of an elaborate defense mechanism for maintaining the anatomical integrity of the upper airways. This anatomical region appears to be a special area, on which various factors could act in predisposing patients to sleep apnea.

In conditions of quiet and normal breathing, the inhaled air proceeds in a well-defined anatomical way, which involves the upper and lower airways. Each obstruction to the physiological progression of the breathed air could be responsible for the so-called obstructive sleep apnea syndromes (OSAS), which include more than 85% of all sleep apneas (Fig. 1). Patients with OSAS may also have some central apneas (CSA), but this is much less common than OSAS.[1] The name respiratory epithelium refers to structural rather than to functional features, since this respiratory gas exchange only occurs in lung alveoli;[2] the respiratory nasal mucosa, which covers the nasal cavities (except for their vestibules, which show keratinizing stratified squamous epithelium), is composed of pseudostratified ciliated columnar cells, with interposed muciparous goblet cells and sparse microvillus and basal cells (Fig. 2). This epithelium overlies a rich capillary plexus, located in the lamina propria. Because the mucous layer is often contiguous with the periosteum or perichondrium, the terms mucoperiosteum and mucoperichondrium are sometimes used (Fig. 3).

The nasal mucosa continues with the nasopharyngeal mucosa through the

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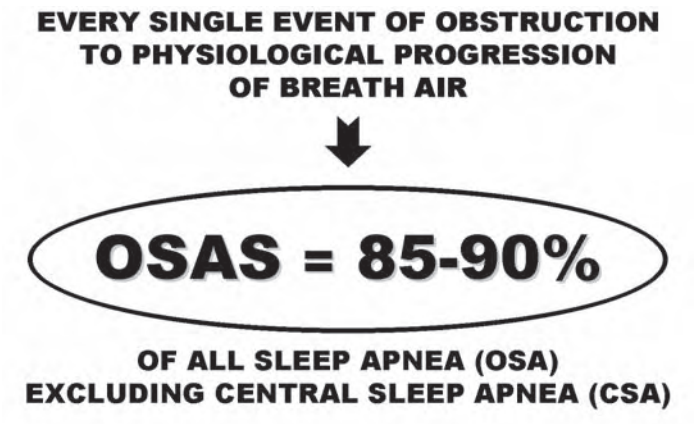


*Fig. 1.*

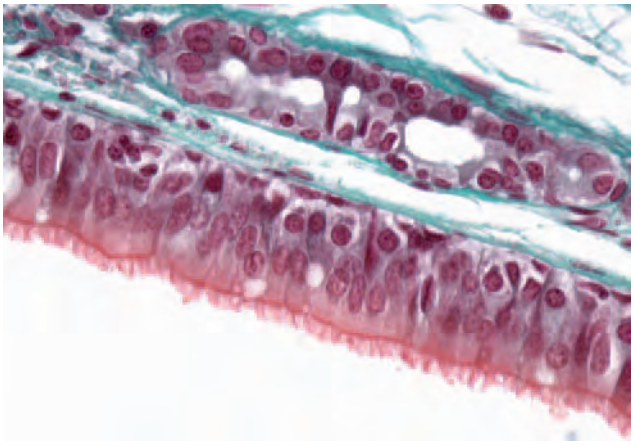

*Fig. 2.* LM (50×). Respiratory nasal mucosa made up of pseudostratified ciliated columnar cells with muciparous goblet cells interposed (original magnification).

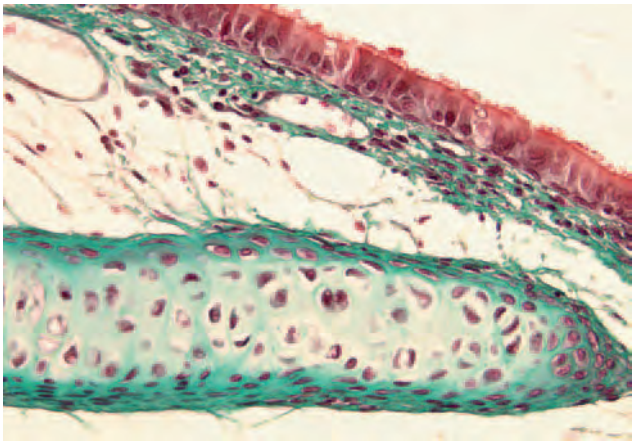

*Fig. 3.* LM (50×). Respiratory nasal mucosa contiguous with the perichondrium (*i.e.*, muco-perichondrium).

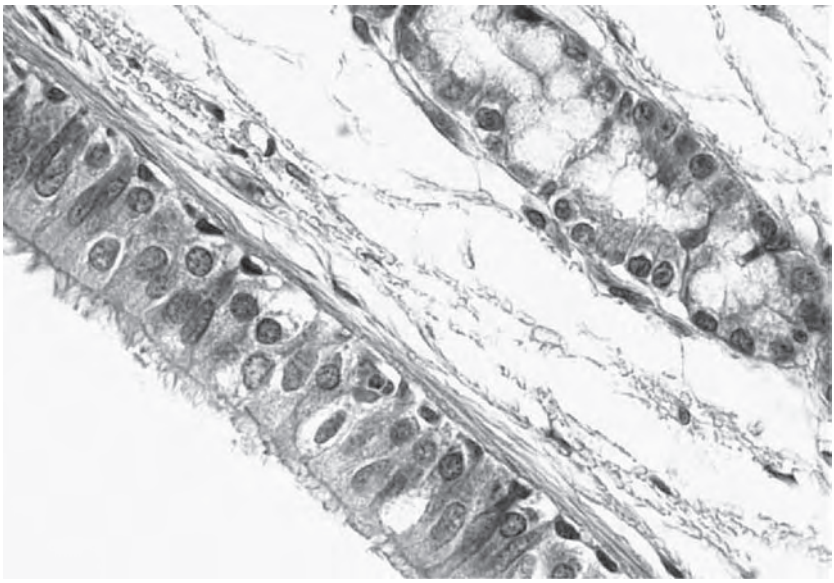

*Fig. 4.* LM (50×). Respiratory nasal mucosa. The propria seromucous glands are visible in the lamina.

conchae, together with the ocular conjunctiva and the mucosae of the sphenoidal, ethmoidal, frontal and maxillary sinuses through their openings.[3]

The mucosa is thickest and most vascularized over the conchae and along the nasal septum, and contains seromucous glands in the lamina propria, but it is very thin in the meatuses, on the floor of the nose, and in the sinuses. Its thickness substantially reduces the volume of the nasal cavities and their perviousness.[4]

The nasal mucosa is normally bathed by a continuous layer of mucus, produced by goblet cells and by glands located in the lamina propria (Fig. 4). The mucus is a viscous gel that lines the entire respiratory tract in a thin layer; the action of the cilia continuously moves the mucus towards the pharynx, where it is usually swallowed or expectorated. The ciliary system has a metachronal rhythm that produces sequential waves; these complex movements are due to very sophisticated intracellular machinery. This consists of specialized differentiation of the cell cytoskeleton, with microtubules linked to intermediate filaments, that reach the basal corpuscles of each cilium. The fine ultrastructural appearance of the cilia lead us to recognize two central fibers linked by nine radial spokes to nine perispherical microtubules doublets, and linked by nexin bridges, with two inner and outer arms.

This complex ciliary system is also involved in trapping extraneous particles, and in adding to the special molecules in the inhaled air, synthesized by the local immune system (lymphocytes, plasma cells and mast cells), located in the lamina propria. This action is complemented by the superficial antimi-

crobial activity of the seromucous secretion of the tubulo-acinar glands also located in the lamina propria, which are rich in IgA immunoglobulin with bacteriolytic properties.

In the deeper stratum of the lamina propria, the nasal mucosa shows a complex network of blood vessels which can be functionally classified as follows: capacitance vessels, resistance vessels, and exchange vessels. Therefore, venous vessels and cavernous sinusoids are involved in regulating the local blood volume, arterioles and arteriovenous anastomoses in modifying the blood flow, whether or not capillaries are involved in the transport through the endothelium of electrolytes and protein molecules.[5]

The arterioles of the respiratory mucosa lack internal elastic lamina. However, they have a basal membrane with pores and interruptions, as capillaries do. This particular finding could explain the reason why many substances that have a powerful action on the blood vessels (*i.e.*, noradrenaline, acetylcholine, histamine, serotonin) are able to induce modifications of the vessels by acting on the smooth muscle cells of the vasal wall.

Since the complex mechanisms that regulate nasal function depend on the anatomical integrity of the nasal structures involved, detailed knowledge of the mucosal vascular architecture is of considerable importance. Methods of injection using polymerizing resins and, in particular, the study of vascular corrosion casts (VCCs) observed by scanning electron microscopy (SEM), now make it possible to gain more insight into the complex mechanisms of thermoregulation and humidification of inhaled air. In fact, the accurate observation of specimens obtained by means of SEM provides details of the nasal microcirculation.

In the septal and lateral parts of the nose, it is possible to identify three vascular layers: the most superficial, located in the subepithelium; the intermediate; and the deepest, composed of vessels supplying the perichondrium and periosteum.

In recent studies, we have also identified different arrangements of the vascular architecture in the human and rat nose.[6,7] A capillary network has been observed within the superficial subepithelial stratum, made up of vessels that are lower in density and fewer in number than the other two layers. The intermediate stratum is formed by rectilinear and parallel vessels and by a dense capillary network, from which small veins branch out and converge to form the cortical stratum (as in the turbinate). These venous vessels form a plexus which contains irregular lacunae with sacciform dilatations, and make up the richly anastomosed venous sinuses.

VCCs have made it possible to identify the nature of the vessel under observation. An initial comparison between veins and arteries can be made by examining casts at low magnification. Veins usually follow an irregular course, while arteries follow a straight one. The difference is confirmed at higher magnifications by observing the imprints of the nuclei of endothelial cells that are rounded in veins, and are spindle-shaped in arteries. On this basis, it is often possible, in the deepest stratum, to identity the arteriovenous anastomoses that appear either as a simple or a complex type.[8]

The above clearly shows that, in the nasal mucosa, we can distinguish two individual vascular systems which can work separately, thanks to arteriovenous shunts: a capillary surface circulation regulating the temperature of the nasal mucosa, and a deep venous plexus on which the degree of turgescence of the turbinates, as well as the total nasal perviousness, depend.

The presence of pericytes at the bifurcation of the thinnest vascular dimensions, and also in the capillary walls, can be clearly seen in semicorroded casts. This explains the very fine regulation of the blood flow, also in the subepithelial capillary network.

The alteration of congestion and decongestion in the deep venous plexus marks the rhythm of the phases of functional rest which, in turn, concern each of the nasal fossa: *i.e.*, the turgescence of the mucosa on one side causes substenosis of the nasal fossa on the same side and, at the same time, increases the perviousness of the one on the other side. In this way, the value of the total nasal resistance tends to remain constant.[9]

The mucosal, vascular, and muscular structures described here are responsive to neural and humoral mediators. Evidence increasingly suggests that the organization of the autonomic nervous pathways is very complex. In fact, a number of biologically active peptides are known to be present in different nerves, and coexist with the classical neurotransmitters, noradrenaline and acetylcholine. However, the release and action of these two transmitters cannot account for all the effects observed on nervous activation. Nerves sympathetic to blood vessels contain neuropeptide Y as well as noradrenaline, and they have a marked effect on blood flow changes, while changes in blood volume at a sinusoid level are due to noradrenaline release. In parasympathetic nerves, acetylcholine coexists with vasoactive intestinal polypeptide (VIP), which is involved in increasing the blood flow, and acts as a neuromodulator of secretory events. Substance P, neurokinin A, and calcitonin gene-related peptide coexist around the blood vessels and within the epithelial lining of the nasal mucosa in a specific population of sensory trigeminal nerves. Also, capsaicin possesses a mechanism of action which selectively activates thin unmyelinated C-afferent fibers, causing the release of their content of substance P.[10]

Structures other than the upper airways could be involved in events that obstruct the progression of the inhaled air. These include the root of tongue in its pharyngeal part and the nasal part of the pharynx including the pharyngeal tonsils.

As is well known, the tongue is partly in an oral and partly a pharyngeal position, and is attached by muscles to the hyoid bone, mandible, styloid processes, soft palate, and pharyngeal wall. The V-shaped *sulcus terminalis*, the limbs of which run from the median *foramen caecum* to the palatoglossal arches, separates the oral (anterior two-thirds) and pharyngeal (posterior one-third) regions of the tongue, which differ in their mucosa, nerve supply, and development.

The pharyngeal (postsulcal) part lies posterior to the palatoglossal arches and forms the anterior wall of the oropharynx. Its mucosa is reflected laterally on to the palatine tonsils and pharyngeal wall, and posteriorly on to the epig-

lottic folds. Except for the papillae, this part of the tongue has low elevations due to the lymphoid tissue organized in nodules and embedded in the submucosa, collectively known as the lingual tonsils. The nasal part of the pharynx is located behind the nose and above the soft palate; its walls are static except for the soft palate and its cavity is never obliterated, thereby differing from the other two parts of the pharynx. Between the border of the soft palate and the posterior pharyngeal wall, the nasal and oral parts communicate through the pharyngeal isthmus, which is closed during swallowing by the elevation of the palate and the contraction of the palatopharyngeal sphincter.

In the upper part of the nasopharyngeal wall, a lymphoid mass known as the pharyngeal tonsil can be found in the submucosa. In an 18-month-old child, this appears as a pyramidal prominence with the apex located near the nasal septum, and the base at the junction of the nasopharyngeal roof and posterior wall. It consists of a fold that radiates from a median blind recess located at the base of the tonsil: the pharyngeal bursa. The mucosal folds are mainly diffuse lymphoid tissue, but also present deep mucous glands.[4]

The lateral prolongation of the pharyngeal tonsil behind the opening of the auditory tube produces a tubal tonsil, consisting of unencapsulated lymphoid tissue. This lymphoid tissue is close to that of the nasopharynx and is especially abundant in the area of the pharyngeal ostium, where it infiltrates the epithelium. During the fetal stage, the lymphoid tissue is made up of isolated lymphocytes, but during childhood, at about the age of four years, the tubal lymphatic tissues also comprise true follicles that regress to atrophy in adults.

In the oropharyngeal region, between the glossopalatin and the pharyngopalatin arches, the palatine tonsils can be found, consisting of two large accumulations of lymphoid tissue, where the overlying pluristratified epithelium invaginates to form ten to 20 tonsillar crypts. The lymphoid nodules, with their prominent germinal centers, are embedded in a diffuse mass of lymphoid tissue, while in the epithelial crypts, the epithelium becomes thinner and more monostratified. The surface features of the cryptal epithelium show the presence of microplicae and some cells that have been termed ‘M cells’. These cells are always in close contact with isolated lymphocytes, and on their luminal membrane show the typical presence of sparse, short microvilli. These cells are also present in the pharyngeal tonsils, and the term M cells is now currently used to describe a distinctive class of cells present in the epithelium, covering mucosa-associated lymphoid tissue (MALT). In fact, M cells have been described in Peyer’s patches, in the appendix, colon, and rectum, as well as in the palatine and pharyngeal tonsils, and the bronchus and conjunctiva. Therefore, the identification of M cells is indeed controversial, as is their origin: microvilli, microfolds, or microplicae; and other features have been proposed as markers for these cells. On the other hand, many experimental and *in vivo* observations suggest that M cells play a fundamental role in antigen transport, under the control of the local immune system. In our opinion, based on experimental studies on rat Peyer’s patches and on human palatine tonsils, the concept that a distinct M cell type

can be identified on the basis of morphological, immunohistochemical, or functional criteria does not appear to be any more valid. Today, it would seem correct that the so-called M cells, characterized by a few short microvilli and closely related to lymphocytes, should rather be considered normal dynamic morphofunctionally shaped cells that are frequently renewed and that show morphofunctional dynamic modifications in their morphology, in relation to their functional state.[11]

In the complex mechanism of breathing, an important role is also played by the respiratory muscles.[12] These are the only skeletal muscles that are essential for life, and have therefore been defined the 'vital pump'. The diaphragm, inspiratory intercostal muscles, and accessory inspiration muscles (the scalenes and sternocleidomastoids) are defined as inspiration muscles and are involved in the active work required for inspiration. On the other hand, expiration in normal, quiet conditions is passive and does not require any exertion, but if there is an increase in ventilatory requirements (for example, in case of chronic obstructive diseases), expiration often becomes an active process. In these cases, the expiration muscles are put to work; these include the internal intercostal muscles and abdominal wall muscles (external and internal oblique, transversal abdominis, rectus abdominis). The increased demands on the respiratory muscles due to airway obstruction and hyperinflation may be an important factor in ventilatory failure.

The pathophysiology of upper airway obstruction is complex and is still under in-depth investigation. Starting from what happens during normal breathing, it is well known that upper airway muscle activity is responsible for maintaining upper airway patency, despite negative intraluminal pressure and positive extraluminal pressure.[13-15] Upper airway muscle activity is implemented by chemical stimuli such as hypoxia and hypercapnia, but also by the presence of negative upper airway pressure that could act as a mechanoreceptor stimulus. Another situation able to augment upper airway muscle activity is activation of the brainstem associated with wakefulness (the so-called 'wakefulness stimulus'), which occurs when the upper airways are stimulated by negative pressure.[14] With the onset of sleep, the wakefulness stimulus is lost and the negative pressure reflex is diminished; thus, within one or two breaths after the onset of sleep, upper airway muscle activity generally decreases and upper airway resistance increases, even in normal subjects. In normal subjects, it has been proved that the major site of narrowing in the upper airways appears to be the retropalatal area.

The patency of the upper airways depends on the extraluminal tissue together with the influence of gravitation factors (such as supine posture), anatomical factors (such as airway size and shape), the amount of negative intraluminal pressure, and the amount of upper airways activity. Moreover, another important factor which influences upper airway patency is tracheal traction: during inspiration, phasic activation of the upper airway muscles and the effects of tracheal traction maintain upper airway patency, despite negative intraluminal

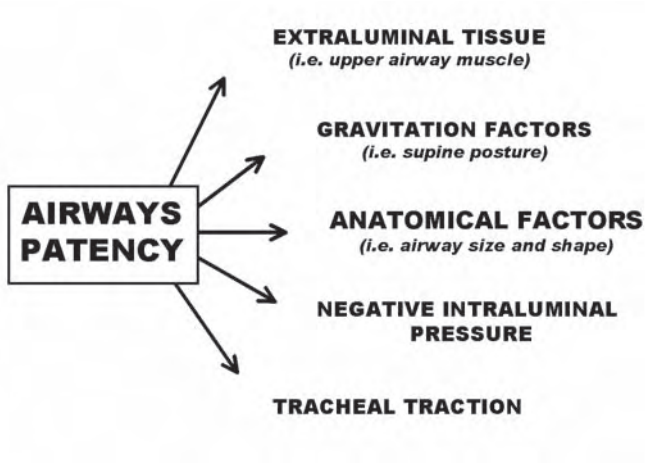


*Fig. 5.*

pressure. If the forces tending to close the airway exceed those maintaining airway patency, airway closure occurs (Fig. 5).

In patients with OSAS, obstruction of airflow, such as extreme narrowing or closure, occurs during sleep at one or several locations in the upper airway.[16] Many studies of the upper airways in awake patients with OSAS using cephalometric radiography, computed tomography, the acoustic reflection technique, and magnetic resonance imaging usually show smaller than normal upper airways.[17]

The pathophysiology of OSAS is complex and not completely understood, but it is principally based on an imbalance between the collapsing forces of the upper airway during inspiration and the counteracting dilating forces of the upper airway dilating muscles. Some OSAS patients show bony abnormalities, while others have long soft palates, large posteriorly placed tongues, increased deposits of fat at the neck or at a systemic level, tissue edema, or adenotonsillar hyperplasia, which all may play a role in the narrowing of the airway. In some cases, the presence of pharyngeal walls which are increased in thickness can also be seen, although this does not explain the fat deposits.

Briefly, considering all these causes of OSAS, and regarding the anatomical bony abnormalities that occur in OSAS, the most common of these involve the anterior floor of the cranial base, the mandible, the posture of the head, and the lower position of the hyoid bone. These anomalies are present in both obese and non-obese patients.[18,19] Obesity is considered to be one of the most important risk factors in the development of OSAS. Therefore, it is likely that craniofacial bony abnormalities play a substantial role in the development of OSAS in less obese patients, as shown in recent studies. These findings may also be due to racial differences in the craniofacial bony structure. Therefore, it is possible that non-obese Japanese patients with OSAS may have many bony structural abnormalities when compared with Caucasian or Hispanic patients. Therefore, it is possible that, in severe OSAS patients, craniofacial bony struc-

tural abnormalities play an important role in the development of OSAS in less obese patients.

Nevertheless, the obese adult patients also show abnormalities in the upper airway soft tissue, especially at the oropharyngeal isthmus level, such as excessive fat deposits in the palate, at the base of the tongue, and at the pharynx wall, causing the epipharyngeal space to become narrow. In these cases, the obstruction is caused by a long soft palate or base of the tongue, or both, collapsing against the pharyngeal walls, due to decreased muscle tone during sleep.

Although the anatomical relationship between structural abnormalities of the oropharyngeal isthmus, such as bony, lymphoid, and other tissues affecting the shape of the upper airway in children with OSAS, has not yet been established, many authors confirm that the volume of the upper airway is smaller in children with OSAS. This is mostly due to large adenoids and tonsils, and to large soft palates, which differ markedly from those in adults.

Also, functional impairment of the upper airway dilating muscles is particularly important in the development of OSAS, especially in adults. These patients show increased upper airway collapsibility due to functional impairment of the upper airway dilating muscles (elevator of veli palatini, palatoglossus, velopharingeal muscles, and genioglossus), which show a reduction in both their tonic and phasic contraction during sleep, when compared to normal subjects.

All the above-mentioned points show that airway size during wakefulness is influenced by both the bone and soft tissue anatomy and upper airway muscle activity; therefore, a higher than normal percentage of maximum upper airway muscle activity is required in order to preserve upper airway patency in OSAS patients.[20]

Thus, as things stand at present, it is possible to state that the upper airway anatomy, in the different compartments we have summarized, and the loss of muscle activity, are the key elements in upper airway obstruction.

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# SOFT PALATE AND VOICING

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The soft palate, considered to be the main structure of the velopharyngeal sphincter, plays a relevant role in voice production and some vocal functions. This happens because, through the opening or closing of the velopharyngeal sphincter, the voice as an acoustic factor produced at the level of the vocal folds undergoes modification mainly of its spectrum by the vocal tract, which differs when it only consists of the hypo- and oropharynx and the oral cavity or when the nasopharynx and nasal cavities are added.[1]

As shown in Table 1, soft palate and voicing has a long history, starting with the appearance of birds and ending with the *Homo sapiens*.[2] In fact, only with birds do we see effective respiratory ventilation, allowing the production of sounds at the level of the syrinx (or afterwards of the larynx), and only in *Homo sapiens* do we see the respiratory and swallowing pathways crossing at the level of the oropharynx, which is completely functional neurologically and is driven by four valves (Table 2).

*Table 1.* Timetable

| *Years ago* | *Event* |
|---|---|
| 15,000,000,000 | Big bang |
| 5,000,000,000 | Birth of the earth |
| 4,000,000,000 | First signs of life |
| 2,000,000,000 | Start of communication (and of sexual reproduction) |
| 400,000,000 | Appearance of the vertebrates |
| n × 10,000,000 | Start of respiratory ventilation and of hearing (especially of acute sounds in some reptiles and especially in birds and mammals). *Voice is born* |
| 4,000,000 | Appearance of primates (apes and hominids) |
| 50,000 | Appearance of *Homo sapiens* and of the spoken language. *Birth of the spoken voice* |
| Up until the present | Progressive flexible modification and growth of vocal ability through culture and education |

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*Table 2.* Phylogeny and purpose of the velopharyngeal sphincter

| |
|---|
| *Phylogeny* |
| some ten million years ago |
| associated with ventilatory respiration |
| *Purpose* |
| regulation of different flows in the alimentary and ventilatory tubes of the pharyngeal crossing |
| one of the four valves of the pharyngeal quadrivium, namely: |
| velopharyngeal sphincter |
| glossovelopharyngeal sphincter |
| glottic sphincter |
| upper esophageal sphincter |

*Table 3.* Relationship with the local structures and functions and parts of the nasal-oral-laryngeal-esophageal quadrivium

| |
|---|
| *Functions* |
| respiratory ventilation (nasal, oral, inspiratory, expiratory) |
| deglutition (sucking, oral preparation, oral, pharyngeal and esophageal aspects, as far as the lower esophageal sphincter; esophageal reflux; vomiting; belching |
| olfaction |
| taste |
| different kinds of reflexes |
| *Structures* |
| osteoarticular (cranial, spinal, thoracic) |
| ligaments |
| muscles |
| neural |

The function and structures of the complex to which the velopharyngeal sphincter belongs are shown in Table 3.

It is very difficult to understand what the voice is: everyone agrees with the acoustic nature of the voice, but its definitions vary from restricted[3] (the voice is each and every sound produced by the activity of the true vocal folds) to very extended (the voice is each and every sonority – either sound or noise – however produced by the person, through any part of the body, *e.g.*, hands – possibly aided by instruments or prostheses).[2] In this presentation, we will use the following definition: "voice is each and every sonority produced either intentionally or unintentionally in the larynx and/or vocal tract suitable for information or communication".

The teleology and heuristics of the voice (Table 4) are rather complex, and we must consider the five points listed therein. Of major importance is the first point, which is strongly related to the existence and personality of each human being: this means that many people identify themselves by their voice (and therefore, a bad or unsatisfactory voice produces bad or unsatisfactory feelings).[2]

*Table 4.* Meaning and scope of the voice

| |
|---|
| *I do exist* and by the voice I manifest my presence, my identity and my location |
| *These are my feelings* (and particularly anger, fear, happiness, love, surprise, disgust, sadness) |
| *The non-verbal messages* |
| the scream or shout |
| the call |
| help |
| the threat |
| the wooing |
| singing |
| etc. |
| *The verbal vocal messages* |
| *The athletes* |
| the speaker (preacher, lawyer, advocate, teacher, etc.) |
| the actor |
| the singer |
| others |

*Table 5.* The velopharyngeal sphincter and vocal utterances

| |
|---|
| *Physiology* |
| nasal voicing |
| nasal vowels |
| special effects (religion, nobility, snob) |
| *Pathology* |
| total or partial velopharyngeal insufficiency (rhinophonia aperta) |
| total or partial absence of the possibility to communicate between oral and nasal cavities (rhinophonia clausa) |
| a mixture of the two (and other cases) |
| Velopharyngeal sphincteral disabilities (normally) have a mainly aesthetic effect on the voice |

As already stated, the soft palate is able to modify the spectrum of the voice. The non-verbal nature of the voice is known as phonia (good voice = euphonia; bad voice = dysphonia). Table 5 presents the principal aspects of the relationship between the soft palate and the non-spoken voice or phonia. Generally speaking, if we notice something in a voice that is thought to do with the 'nose', we talk of a nasalized voice or nasality: however, this label is very ambiguous and imprecise, and can also be related to the opposite situation (*e.g.*, a cold rather than a palatal cleft), which can lead to the wrong treatment. Table 6 presents the various nasality labels (concepts).

The velopharyngeal sphincter is of the utmost importance in building up the different sounds (phonemes) of the phonological systems of different languages. In this case, we are concerned with the verbal articulated voice or lalia (eulalia = good speech; dyslalia = bad speech) (Table 6). A phonetic feature or marker is able to modify the normal acoustic characteristics of a phoneme (speech

*Table 6.* Nasality, or influence of the nasal cavities on resonance (the paranasal cavities play no significant part in nasal resonance)

*Rhinophonia = nasal voice*
  aperta or hyperrhinophonia
  clausa
  mixta
*Rhinolalia = nasal speech*
  aperta or hyperrhinolalia
  clausa
  mixta
*Aperta or Open = more resonance volume* (oral and nasal parts of the vocal tract)
  example: cleft palate
*Clausa or Closed = less resonance volume* (no resonance of the nasal cavities)
  example: a severe cold
*Mixta or Mixed = always partial resonance of the nasal cavities;* sharp separation of the oral and nasal resonances impossible
  examples: velopharyngeal surgery; cleft palate and a cold; cleft palate and functional compensation; cleft palate and inadequate surgery
*Anterior versus Posterior* if the causes can be found in the anterior or posterior parts of the nasal cavities

sound) without it being altered or becoming unrecognizable. On the other hand, dysfunction or impairment of the soft palate can cause a phonological mistake if it leads to the production of a wrong speech sound (*e.g.*, /m/ instead of /b/ or /n/ instead of /d/). Figure 1 shows the different positions of the Italian consonants, especially of the nasal ones. It must be remembered that some languages (*e.g.*, French) have a double series of vowels (oral and nasal), while almost all languages have this double series – oral/nasal – for consonants only.[4]

Table 7 lists the principal aspects of the relationship between the soft palate and articulation, spoken voice, or speech.[5]

*Table 7.* The velopharyngeal sphincter and speech

*Physiology*
  nasal versus oral sounds and phonemes
*Pathology*
  impossibility or difficulty in producing some sounds or phonemes
  distortion of the distinctive features of some phonemes
  pathological sounds (*e.g.*, glottal stops)
  nasal noises
  grimacing

Velopharyngeal sphincteral disability can have important consequences on compensation of speech and language, conversation and, generally speaking, communication

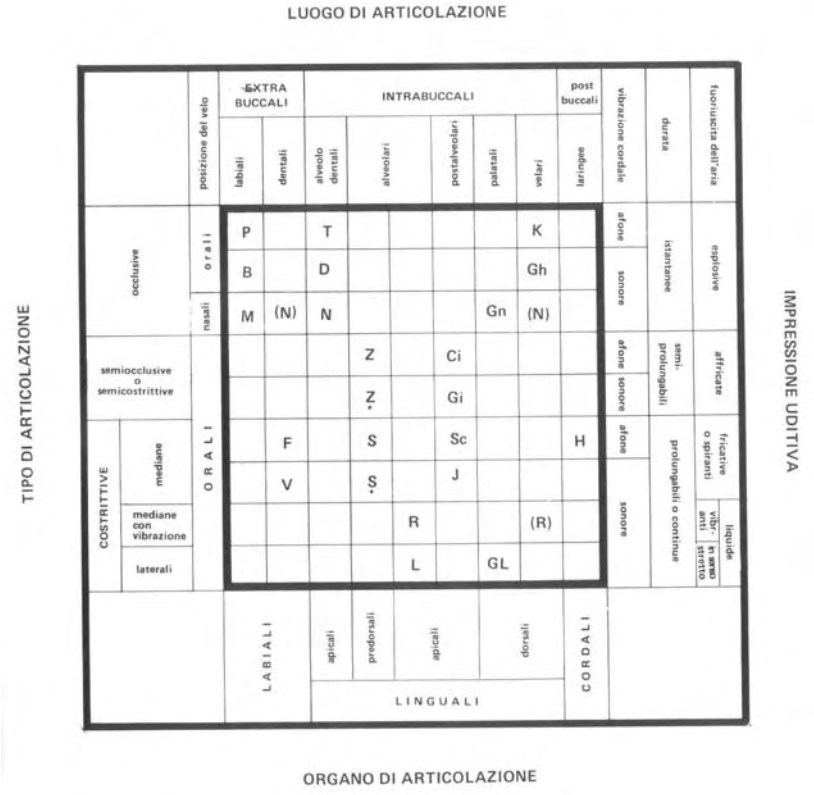


*Fig. 1.* Articulation of the Italian consonants.

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# OBSTRUCTIVE SLEEP APNEA

## A historical survey

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### The identification of a new disorder

In the early 1800s, physicians began to suspect that there might be an association between obesity and daytime somnolence.[1] In 1837, in the *Posthumous Papers of the Pickwick Club*, Charles Dickens described an obese boy named Joe with excessive daytime somnolence.[2] Joe has become the prototype of the obesity-hypoventilation syndrome, and probably suffered from obstructive sleep apnea.

A link between obstructed airways and somnolence was first suspected by the British physician, Canton, in 1889[3] and his French colleague, Lamacq, in 1897.[4] These physicians observed that subjects with excessive daytime sleepiness (labeled 'narcoleptics' at that time) might have upper airways that become obstructed during sleep, leading to periods of suffocation. The word 'Pickwickian' was subsequently coined by Sir William Osler in 1918 to describe such obese, hypersomnolent patients.[5]

### The characterization of obstructive sleep apnea

In 1955, Auchincloss *et al.* described an obese patient with hypoventilation and polycythemia.[6] The following year Burwell *et al.* reviewed and characterized the clinical features of a case of Pickwickian syndrome.[7] A link was thus established between obesity and hypersomnolence, but it was not until after the development of polysomnography that research on obstructive sleep apnea flourished.

In 1965, Gastaut *et al.* documented the presence of repetitive obstructive apneas during polysomnographic recording of an obese Pickwickian patient.[8]

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Shortly thereafter, Schwartz and Escande used cinematographic techniques to definitively demonstrate the obstruction of the oropharyngeal airway in Pickwickian patients.[9] The link between obesity, hypoventilation, daytime somnolence, and upper airway obstruction was now established. The next problem was to establish whether the patients described were suffering from a single distinct syndrome, or whether there were a number of disorders with a common clinical presentation. This problem was addressed in 1972 in the first international meeting on hypersomnia with periodic breathing.[10] It was acknowledged that there are different types of Pickwickian syndrome.

It also became evident that non-obese patients may suffer from airway obstruction during sleep. The latter patients have an inherently narrow upper airway anatomy, predisposing them to obstruction during sleep. These patients were described as having the obstructive sleep apnea syndrome (OSAS). OSAS was then used to describe a person with specific symptoms and signs (daytime sleepiness, cognitive dysfunction, snoring, hypertension, and a narrow upper airway), and a polysomnogram showing upper airway obstruction.[11,12] The Pickwickian syndrome was now exclusively applied to obese patients with hypersomnolence, hypoventilation and hypercapnia, and usually signs of cardiac dysfunction.

The polygraphic pattern of sleep-induced upper airway obstruction was subsequently described in various other neurological, endocrinological, and hematological conditions such as Parkinson's disease and hypothyroidism. OSAS was first described in children in 1976.[13]

## Obstructive sleep apnea syndrome and hypertension

Although a definitive association between OSAS and cardiovascular disease has not yet been determined, OSAS has been found to be an independent risk factor for hypertension.[14] This risk is independent of other factors associated with hypertension (obesity, age, gender, smoking, alcohol consumption, stress, cardiac and renal disease).[15] The exact mechanism is unknown, but the hypoxia associated with apneic events may result in heightened sympathetic activity and, in turn, in hypertension. Other events associated with acute apneas that may lead to increased sympathetic activity are arousals, excessive muscular effort, and intrathoracic blood volume shifts.[16] The nocturnal sympathetic activity leads to sustained daytime hypertension.

## Identification of the upper airway resistance syndrome

In 1982, Guilleminault and colleagues described a group of children with the symptoms of OSAS but without polygraphic apnea and hypopneas. However, these children were found to have increased respiratory efforts during sleep.[17] In 1993, the same group[18] identified a group of individuals with daytime somnolence who did not have apneas, but rather repeated central nervous system

arousals, during sleep. Using esophageal manometry as a measure of respiratory effort, it was noted that such arousals were preceded by increased respiratory effort. To this subgroup of patients, the term upper airway resistance syndrome (UARS) was applied. The typical UARS patient presents with daytime somnolence, is not obese, may or may not snore, but typically has a narrowed upper airway anatomy.

Of interest, hypotension, particularly postural hypotension, seems to be a common finding in such patients, in contrast to OSAS where hypertension is the usual finding. Further studies are needed to delineate any differences between the underlying physiology of these two closely-related disorders.

## Treatment of obstructive sleep apnea syndrome

Therapeutic trials had already begun long before a full understanding of the pathophysiology of OSAS was available. Weight loss had always been a first line recommendation in the obese Pickwickian patient. In 1969, Kuhlo and colleagues showed the effectiveness of tracheostomy in this latter group of patients.[19] Tracheostomy is rarely used today as there are superior treatment options, but it is worth bearing in mind that this is the only treatment modality that uniformly 'cures' OSAS by bypassing the area of obstruction altogether.

On the medical side, Kumashiro *et al.* showed some improvements in OSAS with the administration of the tricyclic antidepressant clomipramine.[20] Ideally, a drug used in the treatment of OSAS should both stabilize the architecture of sleep and enhance upper airway muscle tone, the most important being the genioglossus muscle.[21] Although subsequent studies have not been as impressive, tricyclics were used for a short time in the treatment of OSAS.

The major breakthrough in OSAS treatment started when, in 1981, Sullivan and colleagues successfully treated sleep-induced upper airway obstruction with nasal continuous positive airway pressure (CPAP).[22] With improved mask designs, CPAP became the medical treatment of choice and has remained so to this day. CPAP helps subjective and objective sleepiness, quality of life, mood, and driving performance.[23] The first studies using a placebo CPAP versus CPAP were only performed recently, and have shown that patients on placebo CPAP (CPAP with no air pressure applied) have a 30% subjective symptomatic improvement, but no objective improvement in sleepiness. Therefore, subjective reports of improvement after treatment may not be as reliable as objective evaluation.

In 1990, Sanders and Kern introduced bilevel positive airway pressure systems (BiPAP). BiPAP reduces the amount of air pressure applied in the expiratory phase of respiration.[24] Even though there are no convincing data of any superiority over CPAP, BiPAP is generally tried when high levels of CPAP are required or if CPAP is not tolerable to the patient.

An exciting new advancement in CPAP technology has been the develop-

ment of auto-titrating CPAP machines.[25] These systems automatically adjust applied air pressures to alleviate airway obstruction. In theory, they can obviate the need for an extra night spent in the sleep laboratory determining optimal CPAP pressures. Current studies are promising, and many such systems are already in use among a considerable number of patients with OSAS.

Oral appliances such as mandibular advancement devices have a place in the treatment of OSAS and have been found to improve sleep architecture and the respiratory disturbance index. Such devices appear to be more effective in mild to moderate OSAS.[26] A potential complication limiting the use of such devices is pain or discomfort at the temporomandibular joint.

Finally, the surgical options for OSAS have also seen remarkable changes in the past few decades. With an increased understanding of anatomical factors predisposing to OSAS, surgical options have also increased. Procedures aimed at correcting nasal obstruction can be helpful, but the most common surgical treatment is the uvulopalatopharyngoplasty. Though first proposed by Ikematsu in 1964, it was Fujita *et al.* in 1981 who first performed this surgery in OSAS.[27] Subsequently, techniques such as mandibular osteotomy with genioglossus advancement,[28] hyoid myotomy-suspension,[29] and maxillomandibular advancement osteotomy[30] have advanced the surgical options.

In patients with UARS, nasal CPAP is often poorly tolerated and surgical approaches or dental appliances have been more commonly used.

An exciting new technique called radiofrequency volumetric tissue reduction, currently utilized in the treatment of snoring, may show promise in the treatment of OSAS. This technique involves the application of radiofrequency energy to tissues such as the base of the tongue, soft palate, and the turbinates.[31] The procedure is painless, conducted in an outpatient setting, and causes tissue protein denaturation. The result is a reduction in the volume of the treated area, and potentially an increase in upper airway caliber. When applied to the palate, this technique resulted in a reduction in snoring and sleepiness.[32] Further studies will show whether radiofrequency ablation has a role in the treatment of OSAS.

## Future directions

The field of sleep disorders medicine is new, as is our experience with OSAS. Today OSAS and UARS are grouped under the term sleep-disordered breathing (SDB). There are clearly different factors, and even clinical syndromes, within SDB that induce abnormal breathing during sleep, and their etiology and evolution is not well understood.

It is now accepted that daytime sleepiness and quality of life are important outcome measures in SDB studies. Future avenues of research are likely to focus on improved methods of SDB detection in the general population, ambulatory versus laboratory diagnosis, delineating the possible role of SDB in heart

disease and stroke, and improved treatment modalities, including refined surgical techniques and the potential role of radiofrequency volumetric tissue reduction.

As for today, treatment modalities have significantly improved the quality of life of thousands of patients worldwide and this trend is likely to increase as more treatment modalities become available.

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# CLASSIFICATION OF HEAVY SNORERS DISEASE

## From snoring to sleep apnea syndrome

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### Introduction

For a long time, snoring was merely regarded as a troublesome noise, a nuisance to the snorer's unfortunate bed partner or roommate. However, intermittent snoring, a typical manifestation of obstructive sleep apnea syndrome (OSAS), is an important symptom due to its clinical and pathophysiological implications.

A continuum in severity from asymptomatic snoring (so-called simple snoring) to full-blown sleep apnea syndrome through a slowly worsening disease state, was suggested by the natural history and videopolysomnographical recordings (PSG) of OSAS patients:[1,2] almost all patients with OSAS had been heavy snorers for years or even decades before their symptoms developed.

Snoring, excessive daytime somnolence, and witnessed apneas typically develop insidiously over a period of years, and snoring may precede the onset of sleep apneas by 15-20 years.[3]

Some subjects remain 'simple snorers' all their lives, while others manifest the full-blown disease within a few years. Rapid weight increase favors intermittent snoring and apneas, which are much more common in males. The transformation from simple snoring to typical OSAS takes place between the fourth and fifth decades in males; in females, the transition occurs after the menopause.

The early onset of snoring seems to favor the most severe form of OSAS. In fact, patients who start snoring in the second decade of life are more likely to reach the advanced stage of the disease.

One to two years after the onset of intermittent snoring (apneas), excessive daytime sleepiness, another key symptom of OSAS, generally manifests itself.

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## Associated symptoms

A number of other OSAS-associated symptoms have frequently been described, including gastroesophageal reflux, nocturia or unusually enuresis, abnormal motor activity, and sweating during sleep. Diminished libido and impotence frequently occur in OSAS patients. Nocturnal choking episodes and morning headache are commonly associated symptoms. Worsening of the short-term memory, cognitive impairment, poor concentration, and changes in mood and personality may be also observed in the more advanced stages of the disease.[4,5]

## Heavy snorers' disease

We proposed the term 'heavy snorers disease' (HSD) as a synonym of OSAS in order to emphasize the close relationship between snoring and obstructive sleep apnea.[2] Both these conditions are, in fact, due to stenosis of the upper airways and represent the endpoints of the same disorder: sleep-related narrowing of the upper airways.

Unlike sleep apnea, snoring has a minimal effect upon alveolar ventilation; but, in patients with lung disease or severe obesity, even simple snoring can induce nocturnal hypoxemia.[6]

Ventilatory and circulatory changes, which may be present in snorers, are consistently seen in OSAS patients. Each apneic episode is associated with phasic oxygen desaturation. At the end of each apnea, oxygen saturation returns to baseline levels, whereas heart rate and arterial pressure show a sharp increase.

One of the major controversies in recent years has been the question of pinpointing the passage from heavy snoring to full-blown OSAS. An objective criterion for disease classification appears to be the apnea/hypopnea index (AHI), *i.e.*, the number of apneas and hypopneas per hour of sleep. An AHI of five, as was proposed initially, seems to be too low, because it is close to the physiological values often found in the elderly, without other signs or symptoms of the disease. For this reason, an AHI of over ten has been suggested for defining the onset of OSAS.

An alternative parameter is the amount of time spent by the patient during sleep in a condition of oxygen desaturation under 4% of basal values, but these criteria are sometimes too mechanical and do not correspond to the different clinical patterns of the syndrome.

When retrospectively studying 130 consecutive patients referred to the Sleep Disorder Centre in Bologna for intermittent snoring, we proposed staging of HSD, based on polygraphic criteria.[2] This classification is widely used in our laboratory, and is still valid for clinical purposes. Snoring sickness can be classified into four stages:

- *Stage 0 or preclinical stage:* characterized by habitual snoring with sporadic

or no apneas; snoring is more or less continuous throughout the night and is often related to the patient's sleeping position. In these cases, insufficient sleep and intense and long daytime activity could exacerbate the disease, intensifying snoring and increasing the number of apneas.

- *Stage 1 or initial disease:* snoring becomes intermittent during light sleep (stages 1 and 2 NREM) and REM sleep, particularly in the supine position. Apneas occur in the supine position, when there is a greater tendency for the oropharyngeal muscles to collapse, and during light or REM sleep when the central breathing undergoes physiological phasic oscillations. AHI is > 10 and < 30;
- *Stage 2 or full-blown disease:* recurrent apneas persisting almost throughout the night and during all stages of sleep, irrespective of the patient's position. The corresponding AHI is > 30.
- *Stage 3 or complicated disease:* recurrent apneas persist throughout sleep, as in stage 2. In addition, oxygen saturation fails to return to basal values (tonic drops) during REM sleep and, as a rule, moderate alveolar hypoventilation also occurs during wakefulness.

We also proposed classifying snorers/OSAS subjects into four groups, based on daytime somnolence:

- *Group 0* with a mean sleep latency greater than or equal to ten minutes (normal daytime alertness);
- *Group A* with a mean sleep latency of between ten and seven minutes (borderline sleepiness);
- *Group B* with a mean sleep latency of between seven and four minutes (excessive sleepiness);
- *Group C* with a mean sleep latency of less than four minutes (severe sleepiness).[2]

Comparison between nocturnal breathing and daytime sleepiness confirms that sleepiness does not have a predictable relationship with the number of apneas (AHI), corresponding arousals, or severity of oxygen desaturation. Patients may complain of daytime somnolence and can have an abnormal multiple sleep latency test (MSLT) at any stage of the disease. However, daytime sleepiness with a clearly abnormal MSLT is consistently seen from Stage 2 onwards. However, daytime sleepiness can even be absent in patients with a high AHI index. In many of our patients, drowsiness was always present when they tended to hypoventilate even during wakefulness (Stage 3 of the disease).[5]

The relationship between the two most important symptoms of OSAS, respiratory disorder during sleep and daytime somnolence, remains open and awaits clarification from future research.

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# EPIDEMIOLOGY

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## Snoring

Habitual snoring is a widespread phenomenon. In the first large-scale epidemiological study carried out in the Republic of San Marino, 19% of the general population (24% of males and 14% of females) reported habitual snoring.[1] In another epidemiological study, carried out in Bologna in a sample of 3479 randomly-chosen males aged 30-69 years,[2] every night snoring occurred in 10% of the cases. These data are similar to those from a large-scale study in Finland, in which 9% of males and 3.6% of females reported snoring always or almost always when asleep.[3]

Other studies have reported a higher prevalence of snoring. In a Danish population (1504 patients, aged 30-60 years), Jennum and Sjol found that habitual snoring was reported by 19.1% of males and 7.9% of females.[4] Among 1222 Hispanic-American adults, the prevalence of regular loud snoring was 27.8% in males and 15.3% in females,[5] and snoring was reported by 42% of an unselected population of 6000 people in a Canadian study.[6] According to responses given by their spouses, it was reported that 70% of males and 50% of females were habitual snorers. In a telephone interview, Ohayon *et al.* reported that snoring affected 48% of males and 34% of females;[7] Olson *et al.* reported that snoring affected 52% of the general population,[8] and, in a study in an adult population (aged >18 years) in Spain, Marin *et al.* reported that 63.7% of males and 36.3% of females usually or always snored.[9]

The prevalence of habitual snoring rises with age. In a questionnaire survey in France of 58,162 draftees aged between 17 and 22 years, Billiard *et al.* reported that habitual snoring affected 13.6% of the total sample,[10] and Hui *et al.*, in a population of 1910 university students responding to a questionnaire, reported snoring in 25.7% of cases.[11] However, at the age of 60 years, about 60% of males and 40% of females snore almost every night.[1] After 65 years of age, snoring decreases markedly, especially among males.[2,12]

In conclusion, snoring is a common finding affecting between 10 and 70%

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of any population. It is much more common in males, and its prevalence increases with age until 65 years, and decreases thereafter.

## Obstructive sleep apnea syndrome

The exact prevalence of sleep apneas (OSAS) among heavy snorers is unknown because of the need for polygraphic recordings to determine its presence (Table 1). In Israel, Lavie estimated the prevalence of OSAS to be 3% in a study of 1502 industrial workers.[13] The same prevalence was found in an epidemiological survey conducted in Bologna on a sample of 3479 male every-night snorers, aged 30-69 years, randomly selected to undergo nocturnal polysomnographic recording (apnea/hypopnea index (AHI)): 10).[2] By selecting patients with clinical evidence of OSAS in an at-risk population (3100 males, aged 30-69 years), and by studying a sample by means of polysomnography, Gislason *et al.* found that 1.3% of those interviewed had OSAS (AHI: 5).[14] Marin *et al.* estimated that the prevalence of OSAS in Spanish adults (aged >18 years) was 0.8% for females and 2.2% for males,[9] and in a telephone interview, Ohayon *et al.* reported that 2.4-4.6% of males and 0.8-2.2% females had OSAS.[7]

In a Danish population (1504 patients, aged 30-60 years), Jennum and Sjol reported that 10.9% of males and 6.3% of females presented with a respiratory disturbance index (RDI) ≥ 5 and 1.9% of males and 0.9% of females presented with OSAS (hypersomnia and RDI ≥ 5).[4] Considering an AHI of >20, Kripke *et al.* reported that OSAS affected from 5.4-13.2% of males and 2.1-8.3% of females.[15] Considering an AHI >10 associated with excessive daytime sleepiness, Bixler *et al.* found an OSAS prevalence in the general population of 3.3%.[16] However, in a university student population (1910 subjects) responding to questionnaires, Hui *et al.* estimated that the minimum prevalence of OSAS was 0.1% (RDI ≥ 5).[11]

The incidence of apneas during sleep, especially in males, increased with advancing age: OSAS was commonest between 50 and 59 years of age, with a prevalence estimated at between 3.4 and 5.0%.[2,8] In 76 patients aged from 50 to 70 years, Zamarron *et al.* reported a 6.8% prevalence of OSAS.[17]

Sleep-disordered breathing (SDB) is increasingly being recognized in Asian populations as well. In a study of middle-aged (age range: 30-60 years) Chinese males in Hong Kong, Ip *et al.* found that habitual snoring was reported by 23% of this cohort and was associated with excessive daytime sleepiness, hypertension, and body mass index (BMI).[18] The estimated prevalence of SDB and OSAS at various AHI cut-off threshold values was 8.8% and 4.1% (AHI ≥ 5), 6.3% and 3.2% (AHI ≥ 10), and 5.3% and 3.1% (AHI ≥ 15), respectively. Predictors of SDB were BMI, habitual snoring, time taken to fall asleep, and age.

In middle-aged females, snoring and sleep apnea are both common: the menopause is a significant risk factor for SDB and hormone replacement appears to be associated with a reduced risk. In an Italian population of 365 females

(aged 40-65 years), Ferini-Strambi *et al.* found that, when recorded, 7.1% of the patients snored for more than 50% of the night, 10.7% had an RDI > 9, 7.7% had an RDI between 10 and 19, and 2.2% had an RDI ≥ 20.[19]

Bixler *et al.* reported that clinically defined sleep apnea (AHI ≥ 10 and excessive daytime somnolence) had a prevalence of 1.2% in females.[20] The prevalence of sleep apnea is low in premenopausal women (0.6%) as well as in postmenopausal women on hormone replacement therapy (0.5%), and appears to be exclusively associated with obesity. Postmenopausal women not on hormone replacement therapy had a higher prevalence of sleep apnea than that in premenopausal women (2.7%). It is of crucial importance to establish the prevalence of OSAS in a general population in order to treat the disease and prevent its complications.

*Table 1.*

| *Author* | *Date of study* | *Snoring* | *Sleep apnea* |
|---|---|---|---|
| Lugaresi *et al.*[1] | 1980 | 19% general population<br>24% M<br>14% F | |
| Lavie[13] | 1983 | | 3% M |
| Koskenvuo *et al.*[3] | 1985 | 9% M<br>3.6% F | |
| Norton and Dunn[6] | 1985 | 42% general population | |
| Gislason *et al.*[12,14] | 1987-1988 | 15.5% M | 1.3% M |
| Cirignotta *et al.*[2] | 1989 | 10% M | 3% M |
| Schmidt-Nowara *et al.*[5] | 1990 | 27.8% M<br>15.3% F | |
| Jennum and Sjol[4] | 1992 | 19.1% M<br>7.9% F | 1.9% M<br>0.9% F |
| Olson *et al.* | 1995 | 52% general population | 5.7% M<br>1.2% F |
| Kripke *et al.*[15] | 1997 | | 5.4-13.2% M<br>2.1-8.3% F |
| Ohayon *et al.*[7] | 1997 | 48% M<br>36.3% F | 2.4-4.6% M<br>0.8-2.2% F |
| Marin *et al.*[9] | 1997 | 63.7% M<br>36.3% F | 2.2% M<br>0.8% F |
| Bixler *et al.*[16] | 1998 | | 3.3% general population |
| Ferini-Strambi *et al.*[19] | 1999 | 7.1% F | 10.7% F |
| Zamarron *et al.*[17] | 1999 | | 6.8% general population |
| Ip *et al.*[18] | 2001 | 23% M | 3.1%-8,8% M |
| Bixler *et al.*[20] | 2001 | | 1.2% F |

M: male; F: female

OSAS is frequently reported (from 3-13%), especially in overweight males. The prevalence varies between males and females, and the female predisposition for OSAS increases with the menopause. Hormone replacement therapy markedly reduces the prevalence of OSAS.

*OSAS and childhood*

Upper airway obstruction with snoring or OSAS is common during childhood.[21,22] The prevalence varies between 1 and 43% in international studies (depending on age and the size of the cohort and differences in questionnaires), and adenotonsillar hypertrophy is the most common cause of upper airway obstruction.[21]

*OSAS and obesity*

The frequency of snoring increases with obesity in all published epidemiological studies.[4] Habitual snoring was found to occur in 7% of males and 2.8% of females with a BMI below 27 kg/m$^2$, and in 13.9% and 6.1%, respectively, of those above this level.[23]

In the age range 30-59 years, 16% of thin, 32% of moderately obese, and 45% of frankly obese people are habitual snorers.[1]

Chay *et al.* found that, in obese schoolchildren in Singapore, the prevalence of OSAS was 0.7% and, using discriminant analysis, the estimated prevalence increased to 5.7%.[24]

## Snoring and systemic hypertension

SDB is significantly and independently related to a lower general health status. In particular, several cross-sectional studies support the evidence of an association between habitual snoring and arterial hypertension,[1,3,6,12,25,26] independent of other confounding factors such as obesity, age, and sex.[27] In the San Marino study, the relationship between habitual snoring and hypertension was particularly significant in the age group 41-60 years, in which hypertension was present in 15.2% of habitual snorers and in 7.5% of non-snorers.[1] Following our first reports, several other epidemiological studies have confirmed these findings, and have also established snoring as a risk factor for the heart and circulation.[5,6]

Conversely, many research groups reported a significantly increased incidence of apneas during sleep in hypertensive patients compared to controls, suggesting that OSAS and habitual snoring are very common contributing factors to what is called 'essential hypertension'.[28-30] Thirty percent of 50 hypertensive patients had a high AHI (22.4) during sleep, while apneas were absent or only occasional in the normotensive control group.[28] Williams *et al.*[29] and Silverberg and Oksenberg[30] gauge that about 50% of all patients with essential

hypertension have OSAS. Moreover, undiagnosed apneic snoring appears to be associated with a non-dipper condition (blood pressure levels do not fall at night by an average of 15-20% of the mean daytime level) in a population of patients with essential hypertension.[31] So there is now convincing evidence that OSAS is an independent risk factor for essential hypertension, and that treating OSAS will reduce blood pressure. In a study of 1485 adult patients with sleep apnea (AHI >10), 393 of whom reported using anti-hypertensive medications for more than six months, Lavie and Hoffstein reported that patients with sleep apnea whose blood pressure responded beneficially to treatment, have less severe sleep apneas than those patients whose blood pressure remains elevated despite anti-hypertensive therapy.[32] Therefore, arterial hypertension in OSAS seems to be more resistant to treatment.

The mechanism responsible for hypertension in patients with OSAS is unknown. Studies on the acute effects of apneas and hypopneas on the arterial blood pressure in patients with OSAS show that, during apneas and hypopneas, even in those with small oxygen desaturations (only 1-3%), blood pressure decreased during the event, followed by an abrupt increase in the post-event recovery period, and these studies speculate that these fluctuations may play a role in the pathogenesis of hypertension in these patients.[1,33] Many investigators point to the high sympathetic nervous system (SNS) activity observed in OSAS patients.[34] Others hypothesize that hyperactivity of the peripheral chemoreceptors in the regulation of vascular tone significantly contributes to the pathogenesis of hypertension in patients with OSAS,[35] or suggest that abnormal vascular reactivity in arterioles is associated with increasing levels of endothelin-1.[36]

Since the pioneer study in the Republic of San Marino, many other surveys have appeared in the literature, confirming that both OSAS and habitual snoring are independent risk factors for hypertension, and that the treatment of OSAS reduces the systemic blood pressure. Many authors now hypothesize that sleep-related breathing disorders are common contributing factors to what is called ‘essential hypertension’, although the mechanism of the association is known only in part.

## Snoring and vascular risk

Patients with OSAS are at increased risk for cardiovascular disease, and altered cardiovascular variability, even in the absence of hypertension or heart failure often linked to the severity of OSAS, is a prognostic indicator of cardiovascular events.[5,6,37] A relationship between snoring and cardiovascular events was found in two Finnish studies: in the first, it was noted that, in males aged 40-69 years, snoring was correlated with angina pectoris,[3] and in the second (a three-year prospective study on 388 males aged 40-69 years), Koskenvuo *et al.* found that both heart disease and stroke were more frequent in habitual snorers compared to occasional snorers.[38] The risk of ischemic heart disease associ-

ated with snoring was also independent of BMI, hypertension, and smoking.

An association between habitual snoring and electrocardiographic changes and arrhythmias has been reported.[1,25] Valencia-Flores *et al.* studied the prevalence of sleep apnea and ECG abnormalities in morbidly obese patients.[39] They reported that ECG abnormalities were present in 31% of the patients, and that the risk of cardiac arrhythmias increases in the presence of a severe sleep apnea with serious desaturation. Some case-control studies found a significant association between sleep apnea and myocardial infarction.[1,40] Two hundred successive adult patients entering a medical ward in Helsinki, Finland, were asked about their sleeping habits and snoring;[40] 93% of the 43 patients admitted to hospital for an acute myocardial infarction were frequent or constant snorers. D'Alessandro *et al.* conducted a case-control study on 50 patients with myocardial infarction and 100 controls.[41] Nightly snoring was associated with myocardial infarction, and the effect of nightly snoring was independent of smoking, arterial hypertension, diabetes mellitus, or alcohol consumption.

Whether SDB increases the risk of cardiovascular events, and whether part of this risk is likely to be due to a higher RDI, will be tackled in a future follow-up of the Sleep Heart Health Study, a multi-ethnic cohort of 6440 males and females, over the age of 40 years, conducted in the USA between October 1995 and February 1998, by home polysomnography. In 4991 participants, who were free of self-reported cardiovascular disease at the time of the sleep study, moderate levels of SDB were common, with a median RDI of 4.0.[42]

OSAS is also presumed to be significantly associated with cerebrovascular disease, but there are no consistent epidemiological data providing proof of such a link.

In a retrospective analysis, Schulz *et al.* reported that the prevalence of stroke and transient ischemic attack (TIA) in patients with OSAS (187 consecutive patients with a polysomnographically verified diagnosis of OSAS) was 7%.[43] This rate was lower than those for coronary artery disease and arterial hypertension in the same study cohort (14 and 53%, respectively). The 13 patients with stroke had severe OSAS (AHI: 43 ± 5), and almost all of them suffered from arterial hypertension. The mean latency period between the occurrence of stroke or TIA and the diagnosis of OSAS was 41.9 ± 11.3 months.

Habitual snoring and sleep apnea are certainly associated with an increased risk of cardiovascular and cerebrovascular disease. However, to date, there are no clear epidemiological data on the exact prevalence of this association, and it is not known whether this is an isolated risk or whether it is due to the often concomitant hypertension found in these patients.

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# PATHOPHYSIOLOGY

# NEUROLOGICAL CORRELATIONS IN NEUROLOGICAL BREATHING DISORDERS

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> "*To breathe regularly and smoothly at night is not only socially correct but also healthy*"
>
> Antonio Culebras (*Stroke*, 2001:1277)

Sleep-related breathing disorders (SRBD) are made up of habitual snoring, increased upper airway resistance syndrome, periodic breathing, and sleep apnea disorder. Obstructive sleep apnea syndrome (OSAS) is defined as cessation of airflow due to collapse of the upper airway for at least ten seconds. Hypopnea is defined as a reduction in air flow rate with oxygen desaturation. Significant sleep apnea disorder is present when there are > 5 episodes of apnea or hypopnea per hour of sleep (respiratory disturbance index (RDI)). However, a clinically significant condition is considered to be present when there are > 10 events of apnea or hypopnea per hour of sleep. OSAS is a condition characterized by repetitive obstruction of the upper airway, often resulting in oxygen desaturation and arousal from sleep. The majority of patients suffer from excessive daytime sleepiness and tiredness, with neuropsychological dysfunction in the form of poor work performance. Memory impairment, slowed thinking, and headache could be also present, especially in the early hours of the day.

These disturbances are not simply subjective. By means of P300, an event-related potential used to measure cognitive performance, a significant delay of the P300 wave (Fig. 1) has been shown in patients with OSAS.[1] These authors found that, during nasal continuous positive airway pressure (CPAP) treatment, P300 latency was significantly shortened in patients aged less than 45 years, while elderly patients did not show any statistical changes. P300 latencies might be prolonged due to nocturnal hypoxia induced by OSAS, and the abnormality could be irreversible, especially in elderly patients. Furthermore sleepy, male snorers have an increased risk of occupational accidents or motor vehicle crash.[2-4] Early identification and treatment of sleep-disordered breathing may

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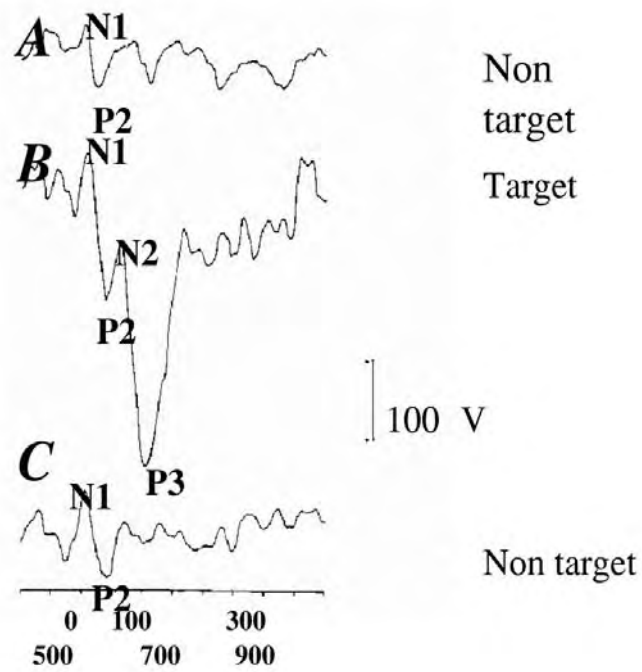
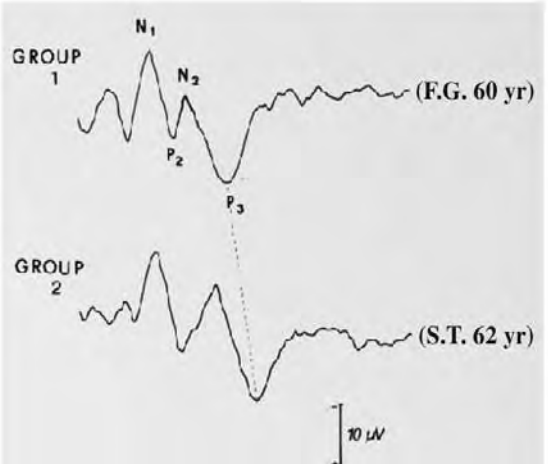



a.




b.

*Fig. 1. a.* P300 healthy adult, 35 years. *b*. P300 in the patients with severe sleep apnea syndrome. Note the significantly longer latency of P300 in sleep apnea patients (group 2) compared with controls (group 1).

reduce the number of injuries at work. Sleep-related breathing disorders, plus related insomnia, are significantly associated with more psychiatric disorders, especially depression, and cognitive-emotional symptoms.

The occurrence of OSAS is usually preceded by a long history of snoring, and the diagnosis is anamnestic: the patient could be aware of snoring, but not of sleep apnea. It is the partner who becomes alert to the interruption of breathing during sleep and asks for a consultation.

The reported prevalence of OSAS in the adult population ranges from 2-10%, depending on various epidemiological studies. In the USA, 18 million people are reported to be suffering from sleep apnea, with a prevalence of 3.9% being seen in males, and of 1.2% in females: so that the male:female ratio of OSAS is 3.3:1 ($p$ = 0.0006). Interestingly enough, in premenopausal women, the prevalence of sleep apnea is 0.6%, the same is seen in postmenopausal women on hormone replacement therapy (HRT; 0.5%). In postmenopausal women without HRT, the prevalence is 2.7%.[5] So, changes in hormones seem to play a pivotal role in the development of OSAS in postmenopausal women.

Furthermore, increasing evidence suggests that snoring and sleep apnea are associated with cerebrovascular diseases. Accumulating epidemiological evidence on the harmful long-term effects of OSAS appears to be related to increasing vascular morbidity and mortality. Several other factors may be involved in this association since many established or potential risk factors for stroke are related to snoring and sleep apnea. These include arterial hypertension, coronary heart disease, age, obesity, smoking, and alcohol consumption, but snoring can also increase the risk of stroke, independent of these confounding factors. Potential mediators among snoring, obstructive sleep apneas, and stroke include cardiac arrhythmias and other hemodynamic disturbances, increased levels of catecholamines, and disturbances in the cerebral blood flow caused by sleep apnea, as well as hypoxemic periods that may potentiate atherosclerosis.

One of the first relevant case-control studies in this field showed that the relative risk for stroke was 10.3 (95% CL, 3.5-30.1) compared to non-snorers (Table 1).[6] In another case-control study of 177 subjects with a mean age of 49 years, Palomaki found a significant increase in the relative risk of stroke with an odds ratio of 8.0 (95% CL, 1.07-356.1) in individuals with a history of sleep apnea after correction for coronary heart disease, hypertension, obesity, or alcohol consumption.[7] The association between snoring and brain infarction was found in all patient subgroups with stroke of probable cardiogenic or atherothrombotic origin, and in those with infarction in the carotid and vertebrobasilar regions. The strength of the association (estimated relative risk) was of the same order as that seen with other stroke risk factors, such as hypertension (95% CL, 4.0-5.0), cardiac disease (95% CL, 2.0-4.0), smoking (95% CL, 1.5-2.9), diabetes mellitus (95% CL, 1.5-3.0), and hyperlipidemia (95% CL, 1.0-2.0) In addition, the risk of stroke is further enhanced because of the high prevalence of hypertension in patients with SRBD.

*Table 1.* Relative risk of stroke in sleep-related breathing disorders

| *Study* | *Design* | *Number of subjects* | *Mean age (yr)* | *SRBD* | *Relative risk (95% CL)* |
|---|---|---|---|---|---|
| Koskenvuo *et al.,*[6] 1987 | Prospective | 4388 | 40-69 | Snoring | 2.38<br>2.08 |
| Partinen and Palomaki[7], 1985 | Case-control | 50 | 54.3 | Always snoring | 10.3 |
| Spriggs *et al*,[8] 1992 | Case-control | 400 | 72.5 | Snoring | 3.20 |
| Palomaki,[9] 1991 | Case-control | 177 | 49 | Snoring<br>OSA | 2.13<br>8 |
| Neau *et al*.,[10] 1995 | Case-control | 133 | 60.6 | Habitual snoring | 3.37 |

The prevalence of sleep-disordered breathing after stroke has been reported to be between 32 and 71%. The strong association between sleep apnea and stroke is supported by a number of studies examining the prevalence of sleep apnea in patients with recent stroke or transient ischemic attacks (Table 2). A high prevalence of OSAS (80%) was demonstrated in a group of patients recovering from hemispheric stroke with no previous history of sleep apnea, compared to age-matched patients with a similar frequency of hypertension and smoking without stroke.[11] Dyken *et al.* presented a similar study, in which 77% of males and 64% of females with stroke had OSAS compared with age-matched controls.[12] In a larger study of 128 patients with transient ischemic attack and stroke, Bassetti and Aldrich found obstructive sleep apnea in 62.5% of patients compared to 12.5% in the group of normal controls.[13] They observed a high frequency of OSAS in patients with transient ischemic attack, suggesting pre-existing OSAS before the cerebrovascular event, rather than as a consequence of it. This latter observation strongly supports the role of sleep apnea as an independent risk factor for cerebrovascular accident.

More recently, studies were devoted to analyzing the presence of SRBD in the first 24 hours after stroke, when upper airway obstruction may have a critical effect on the cerebral circulation, due to hemodynamic fluctuations and repetitive hypoxia. The majority of patients had upper airway obstruction as their main form of SRBD. Only 9% had more central than obstructive sleep apnea. The upper airway obstruction was significantly more severe when patients were nursed in the supine position than in any other position. Measures of obesity were the best predictors of upper airway obstruction after stroke. Stroke characteristics (severity, clinical subtype, and clinically assessed pharyngeal function) are not independently associated with upper airway obstruction after stroke.[14] According to Iranzo *et al*., 62% of patients in their group had sleep apnea on the first day after stroke.[15] Sleep apnea was related to early neurological worsening and oxyhemoglobin desaturation, but not to sleep history before the onset of stroke, or functional outcome.

Regardless of whether sleep apnea precedes or follows a stroke, it is associ-

*Table 2*. Sleep apnea in cerebrovascular disease

| *Study* | *Population* | *Mean age (yr)* | *Incidence of sleep apnea (%)* | *RDI* |
|---|---|---|---|---|
| Mohsenin and Valor,[11] 1995 | Hemispheric stroke | 56.0 | 80% RDI ≥ 20 | 52 ± 31 |
| Dyken *et al*.,[12] 1996 | Recent stroke | 64.7 | 77% RDI ≥ 10 | 22 ± 14 |
| Good *et al*.,[16] 1996 | Ischemic stroke | 69.0 | 95% RDI ≥ 10<br>68% RDI ≥ 20 | 36 ± 23 |
| Bassetti and Aldrich,[13] 1999 | Stroke, TIA | 59.0 | 63% RDI ≥ 10<br>31% RDI ≥ 30 | 28 (0-140) |

ated with a poor functional outcome in survivors and higher mortality after one year, compared to those patients with stroke but without apnea during sleep. The high prevalence of OSAS and poor functional outcome in stroke should prompt physicians to evaluate patients for underlying sleep-related breathing disorders.

There are several pathophysiological mechanisms that may underlie the diurnal development of stroke. Alteration of cerebral hemodynamics, hypoxemia, and dysfunction of cerebral autoregulation appear to be the main mechanisms of cerebral ischemia in patients with SRBD.

Several studies, using a variety of methods including transcranial Doppler ultrasonography, $^{133}$Xe inhalation, and single-photon emission CT, have shown a 5-28% reduction in cerebral blood flow during non-rapid eye movement (n-REM) sleep and a 4-41% increase in REM sleep compared with wakefulness in normal persons. Changes in cerebral blood flow parallel changes in the brain metabolic rate and oxygen consumption in both n-REM and REM sleep. The exception to this is during the transition to and from sleep. These changes in cerebral blood flow are independent of extracerebral hemodynamic factors.

Large fluctuations in cerebral blood flow during and after apnea have been seen: decreased regional cerebral blood flow was seen during the awake state and a significantly greater reduction in brainstem and cerebellum during n-REM sleep.[17] Simultaneous monitoring of intracranial pressure, intra-arterial blood pressure, and central venous pressure in patients with OSAS demonstrated a marked increase in intracranial pressure and a decrease in cerebral perfusion pressure during obstructive apneas (Jennum and Borgesen[18]). The decrease in arterial blood pressure (secondary to more negative intrathoracic pressure) and gradual rise in intracranial pressure during apnea result in decreased cerebral perfusion pressure. Although there was some degree of vasodilation due to hypercapnia and hypoxia during apneic episodes, cerebral perfusion pressure decreased. The magnitude of increased intracranial pressure was linearly related to the duration of apneas. Abnormalities in the cerebral vascular response to hypercapnia have been found in patients with sleep apnea during wakefulness, suggesting impaired cerebral autoregulation.[19]

Reduction in mean and systolic cerebral blood flow velocities of the middle cerebral artery has been also seen in patients with OSAS.[20-22] The reduction in cerebral blood flow was related to the duration of apneas and the degree of oxygen desaturation. Pronounced cerebral blood flow velocity changes during apneic episodes and the concomitant alterations of vessel wall tension might lead to chronic strain on the brain vessels and formation of atherosclerosis.

The fluctuation in cerebral blood flow closely correlated with arterial blood pressure, indicating that cerebral autoregulation is insufficient to protect the brain from rapid systemic pressure changes in OSAS. Patients with OSAS have diminished cerebral vasodilator reserve, which can further impair the ability of the cerebral vessels to adapt to the metabolic needs of the brain. This abnormality is corrected by the treatment of sleep apnea with CPAP, suggesting a functional impairment, as opposed to structural changes in cerebral hemodynamics due to sleep apnea.[23] Another study using ultrasonographic examination investigated whether patients with OSAS have increased atherosclerosis indicators at the carotid artery level. The intima-media thickness of the common carotid arteries of patients with OSAS was significantly higher ($p < 0.0001$) than that of control subjects ($1.429 \pm 0.34$ versus $0.976 \pm 0.17$ mm). An increase in the thickness of the carotid artery wall is a valid marker of the risk of stroke. This finding supports the hypothesis that patients with OSAS are at risk of developing cerebrovascular diseases, regardless of the association with other vascular risk factors.[24]

Even if the pathophysiological mechanisms leading to increased vascular risk in OSAS are still a matter of debate, and many putative causes still being discussed, relative morning hyperviscosity could be one of the leading mechanisms of cardiovascular morbidity which is actually known to be especially high in the early morning. Whole blood viscosity, hematocrit, and plasma fibrinogen concentration (independently of hematocrit changes), increased significantly in the early morning in OSAS patients, but not in healthy controls. This condition could be related to the increased susceptibility for cerebral ischemia in patients affected by OSAS, particularly evident in the early morning.[25]

Platelets play an important role in the pathogenesis and triggering of acute cardiovascular syndromes. Some authors found a correlation between the apnea/hypoapnea index and the platelet activation in the morning,[26,27] but the influence of OSAS on platelet function is not yet fully understood. Platelet aggregation *in vitro* induced by epinephrine showed a slight increase overnight in the untreated OSAS patients, whereas it decreased slightly in the controls and in the treated OSAS patients. Sanner *et al*. suggest that OSAS contributes, at least in part, to platelet dysfunction, and that long-term continuous positive airway pressure treatment may reduce platelet aggregability.[28]

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# PATHOPHYSIOLOGY OF OBSTRUCTIVE SLEEP APNEA SYNDROME

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## Introduction

Obstructive sleep apnea syndrome (OSAS) is a disorder in which people stop breathing during sleep and have signs and symptoms related to the episodes of cessation of breathing.[1] OSAS is found in about 4% of males and 2% of adult females, making it a fairly common disorder.[2] It is astonishing that such a common medical problem was only first recognized by the medical profession about 35 years ago when some early reports described what was then thought to be a very rare condition. One of the reasons for this paradox is that OSAS is a complex disorder in which the abnormal physiology occurs during sleep, and furthermore, the abnormal physiology spans several organ systems.

OSAS is only one of the obstructive sleep breathing disorders. There is a very broad spectrum of these disorders. These range from asymptomatic snoring to upper airway resistance syndrome,[3] to OSAS,[1] and to obesity hypoventilation syndrome.[4,5] All these disorders have a common thread – an increased resistance to airflow in the pharyngeal passage or upper airway during sleep. Patients with OSAS may have repetitive apnea and/or hypopnea episodes; thus, the term obstructive sleep apnea-hypopnea syndrome has also been used to describe them.[1]

In this chapter, we will focus on the pathophysiological mechanisms of upper airway obstruction during sleep, focusing on gas exchange, cardiovascular function, and the state of the central nervous system, and will present the reader with a pathophysiological framework to understand and treat OSAS and its related disorders.

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## The pharyngeal passage

Most people have no problems breathing when they go to sleep. Patients with OSAS develop repetitive complete occlusions of the upper airway (apnea), or reductions in ventilation because of increased airway resistance (hypopnea) during sleep. These patients generally have no problems breathing while they are awake, and thus the sleep state puts their airways at risk. In this section, we will review the pathophysiological mechanisms that play a role in the development of the obstructive geometry of the upper airway, thus increasing the risk of upper airway obstruction, and the mechanisms that restore ventilation.

The pharyngeal passage is divided into the nasopharynx, velopharynx, oropharynx, and hypopharynx. If the only role of the pharyngeal passage were to transfer air in and out of the lungs, a semi-rigid structure like the trachea would be ideal. However, the pharyngeal passage is used for three critical functions in humans:

- breathing, to maintain gas exchange;
- swallowing, to facilitate movement of liquids and solids from the pharynx to the esophagus;
- phonation.

Thus, this part of the anatomy is far more physiologically complex than a simple tube like the trachea. To subserve the latter two functions, it cannot be rigid. In addition, this part of the anatomy, in order to meet its diverse physiological functions, is controlled by complex neuromuscular systems. These systems may not be sufficient to maintain consistent airway patency during sleep, especially if an anatomical obstruction is present. We will now review several interrelated factors which can lead to the geometric changes in the pharyngeal passage that increase the risk of obstruction.

## Interrelated pathophysiological factors playing a role in causing obstruction

### *Intraluminal pressure*

A non-rigid tube such as the pharyngeal passage responds to the difference in pressure between the inside and the outside of the tube. When there is a relative increase in intraluminal pressure (as would occur during the expiratory phase of breathing), the airway tends to enlarge. When there is a relative reduction in intraluminal pressure (as would occur during the inspiratory phase of breathing), the airway tends to decrease in size and may collapse if the intraluminal pressure is sufficiently negative.[6]

### *Anatomical upper airway obstruction*

Anatomical abnormalities of the upper airway predispose to the development of OSAS.[7] Obstructive lesions anywhere in the upper airway from the external

nares to the larynx have been described as causing OSAS. When the airway is obstructed, in order for airflow to occur into the trachea, the intraluminal pressure becomes more negative; that in turn facilitates collapse of the airway at its most vulnerable point, usually the pharynx. Thus, nasal obstruction can induce pharyngeal obstruction by this mechanism.

The range of anatomical abnormalities that can lead to OSAS are reviewed elsewhere in this volume, but a few deserve mention here. First, enlarged tonsils and adenoids are common causes of sleep apnea in children, but can also occur in adults. The vast majority of patients with OSAS are obese, and the exact mechanism whereby obesity leads to obstruction of the upper airway has not been entirely elucidated. Such patients have a 'crowded pharyngeal airway'. Patients with retrognathia and other jaw abnormalities may have no problems in breathing during wakefulness, but may develop profound and severe apnea during sleep. Thus, the mechanisms that maintain airway patency in these patients are adequate during wakefulness, but during sleep these mechanisms are no longer consistently able to maintain airway patency. Even in the absence of significant upper airway anatomical abnormality, the geometry of the upper airway may change sufficiently to cause an increase in upper airway resistance or even complete occlusion of the upper airway.

*Sleep, neck and jaw position*

The supine position predisposes to functional upper airway obstruction.[8,9] Episodes of apnea may be more severe when the patient is flat on his or her back. This has even been observed in patients with mild sleep breathing abnormalities, *e.g.*, the upper airway resistance syndrome.[10]

When the jaw is opened, there is posterior movement of the mandible and posterior movement of the tongue, which would tend to reduce the size of the upper airway. On the other hand, in the presence of macroglossia, or a tongue that is too large for the oral cavity, the optimal size of the pharyngeal airway might be achieved if the jaw were open.[11] Flexion of the neck tends to reduce the size of the airway, while extension of the neck tends to increase the size of the airway.

*Loss of upper airway muscle tone*

More than 20 muscles surround the pharyngeal passage. When the muscles contract, the airway is dilated and its walls stiffen, reducing resistance to airflow.[11] When these muscles lose tone, the airway decreases in size and the walls lose their stiffness, increasing resistance to airflow. It is clear that changes in the tone of the upper airway muscles during sleep play an important role in promoting upper airway obstruction. Alcohol[12-14] and some medications, *e.g.*, benzodiazepines,[15] may also reduce the tone of the upper airway muscle and make the pharyngeal passage more susceptible to collapse during inspiration.

As will be outlined below, reduction in upper airway muscle tone caused by the sleep state, particularly rapid eye movement (REM) sleep, plays an important role in promoting an increase in upper airway resistance.

Sleep in humans is divided into REM and non-rapid eye movement (NREM), which is further subdivided into stages 1 to 4. Normals will spend approximately 5% of the night in stage 1 sleep, 45% of the night in stage 2, 25% of the night in stages 3 and 4, and 25% of the night in REM sleep.[16] Stages 3 and 4 are frequently combined and called slow wave sleep. REM sleep is a state in which there is a mixed frequency in EEG, associated with a dramatic reduction and abolition of muscle tone and the presence of rapid eye movements. During the entire state of REM sleep, there is a background of reduction of muscle tone (paralysis) of most skeletal muscle groups of the body, including the upper airway dilators. This has been called the tonic phase of REM. On top of the background of tonic REM, there occur clusters of eye movements and during these eye movements (phasic REM), many instabilities in physiological control can be demonstrated. For example, heart rate and blood pressure can both become unstable and active thermoregulation may cease during phasic REM.[17] Phasic REM correlates with the generation of waves originating in the pons (pontogeniculooccipital (PGO) waves).

It has been demonstrated that the control of breathing changes during sleep with blunting of hypoxic as well as of hypercapnic ventilatory responses.[18] During NREM sleep, ventilation is primarily controlled by a system that responds to chemical stimuli. $PO_2$ is sensed in the carotid body; $PCO_2$ is sensed both in the carotid body and specialized cells in the brainstem. Outputs from these sensors go to the breathing 'pacemaker', made up of specialized cells in the medulla oblongata.[19] During REM sleep, there may be extreme blunting of the ventilatory responses to $CO_2$ and $O_2$. During phasic REM, there may also be inhibition of the diaphragm motoneurons.[19]

The sleep and arousal state is clearly an important factor in the patency of the upper airway. During wakefulness, patients with even severe sleep apnea usually have no problems in breathing. Even in normals, there is an increase in upper airway resistance (of about five-fold) during sleep compared to wakefulness.[20,21] In snorers, upper airway resistance increases even more to values exceeding 50 $cmH_2O$ per liter per second.[22,23] In patients with apnea, resistance reaches infinity when their upper airways are completely collapsed. It is likely that these changes reflect decreases in neural output to some of the critical upper airway muscles that maintain airway patency. Indeed, it has been shown that reduction in pharyngeal muscle activity (*e.g.*, in the genioglossus and tensor palatini) occurs in the transition from the awake state to sleep. As mentioned above, sleep is not a uniform state. During REM sleep, there is a profound loss of muscle tone in most of the skeletal muscles and there occurs a dramatic reduction in tone (paralysis) of the upper airway muscles. In addition, perhaps in part related to the blunted chemical drive to breathe during REM sleep, and abnormal arousal responses (see below), apneic episodes dur-

ing REM sleep are about ten seconds longer than in NREM sleep, and are associated with more severe hypoxemia.

## Pathophysiological factors reversing upper airway obstruction

### *Reversal of abnormal geometry*

For breathing to resume during an apneic episode, there must be an increase in the tone of the upper airway to reverse the abnormal geometry that has put the airway at risk. What seems to be critical in reversing this process is an arousal – a short awakening measurable by EEG which results in an increase in upper airway muscle tone, re-establishment of a patent airway, and resumption of ventilation. Thus, an understanding of sleep state and arousal is critical in the understanding of how the airway is put at risk, and how airflow is re-established.

### *Arousals and apnea termination*

Arousals, brief awakenings from sleep, restore airway patency and the resumption of ventilation.[24] The physiological mechanisms leading to arousals are not entirely clear. Although it would seem intuitive that hypoxemia is an important cause of arousals, research does not strongly support this hypothesis. For example, it has been shown in normals that hypoxemia is a very unreliable arousal stimulus, and even in the presence of severe hypoxemia, people might not arouse at all.[25] Patients with upper airway resistance syndrome might have many arousals in the absence of measurable hypoxemia.[23] Hypercapnia is a more reliable arousal stimulus in sleeping normals.[26,27] It has been suggested that hypoxemia may increase the sensitivity to arousal from hypercapnia.[28] However, it is unlikely that the $PCO_2$ changes sufficiently during short apneic episodes for this to be the primary arousal stimulus. It has been suggested that it is not the level of hypercapnia or hypoxemia that is critical, but rather the work of breathing itself, which is the stimulus, that causes arousal.[27] Nevertheless, whatever the mechanism, arousal from sleep results in physiology shifting from ‘sleep’ to ‘awake’, with a resulting increase in the chemical drive to breathe for both hypoxia and hypercapnia, and motor output to the muscles of the pharyngeal passage.

In normals, when the upper airway is occluded, arousal from REM is more rapid than from NREM.[25] This situation is reversed in patients with OSAS. Because of the abnormal arousal responses and blunted chemical drive to breathe, apneic episodes during REM sleep are more severe. Medications such as the opiates and benzodiazepines may also blunt arousal responses.

**Acute consequences of sleep disordered breathing** (see Figs. 1-3)

*Gas exchange consequences*

When breathing ceases or there is hypoventilation, a drop in $PaO_2$ occurs as well as an increase in $PaCO_2$. Because of the sigmoid shape of the oxyhemoglobin dissociation curve, when a patient starts off well oxygenated, on the upper flat portion of the oxyhemoglobin dissociation curve, $PO_2$ has to drop a great deal before $SaO_2$ drops a significant amount (see Fig. 4). Conversely, if a patient is already hypoxic at the start of apnea (on the steep portion of the oxyhemoglobin dissociation curve), a similar drop in $PO_2$ may be associated with a rather large drop in $SaO_2$. Thus, the degree of oxygen desaturation is not simply a function of the duration of apnea, but of the level of oxygenation at the start of apnea. The latter may be affected by many variables including oxygen stores (the smaller the oxygen stores and lung volume, the greater the drop in $SaO_2$), airway closure (obese patients frequently ventilate at low lung volumes with a propensity to have closure of small airways at the lung bases), and underlying lung disease. In general, the more obese the patient, the greater the baseline hypoxemia that might be expected.

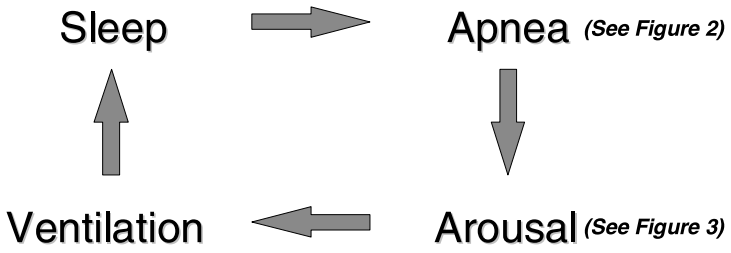


*Fig. 1.* The apnea ventilation cycle: patients with sleep apnea develop apnea when they fall asleep and have an arousal, which terminates the apneic episode

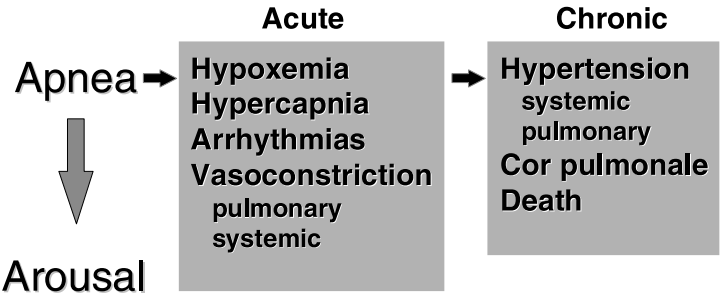


*Fig. 2.* Consequences of apnea: apnea results in hypoxemia, hypercapnia, and cardiovascular system changes.

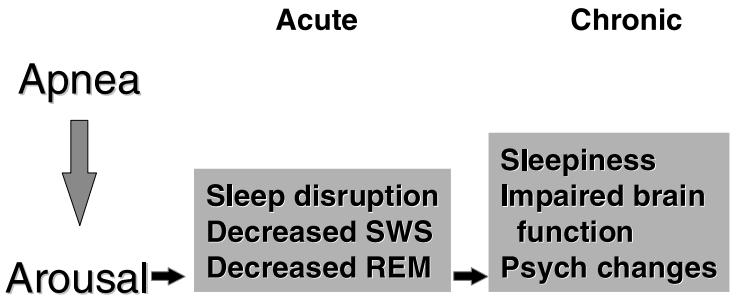


*Fig. 3.* Consequences of arousal: arousals result in neuropsychiatric consequences as marked sleep fragmentation and a reduction in slow wave sleep, resulting in daytime sleepiness.

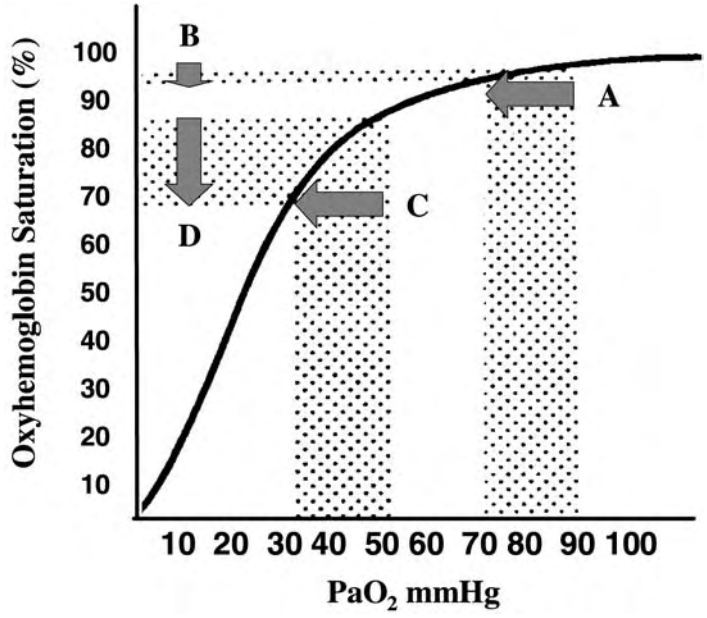


*Fig. 4.* The oxyhemoglobin dissociation curve: when a patient is well oxygenated and on the flat part of the oxyhemoglobin dissociation curve, a 20 mmHg drop in $PO_2$ (A) results in a small drop in $SaO_2$ (B); when a patient is already hypoxic, a similar 20 mmHg drop (C) in $PO_2$ results in a larger drop in $SaO_2$ (D).

Apnea duration, oxygen stores in the lung, and carbon dioxide stores in the body determine the degree of hypoxemia and hypercapnia that occur with apneic episodes. The lower the oxygen stores, as may occur with low lung volumes related to obesity or lung disease, the greater the oxygen desaturation. Because of the much greater body stores of carbon dioxide than oxygen, an apneic episode results in a much larger reduction in $PO_2$ than an increase in

$PCO_2$. Thus, with a one-minute breath hold, $PCO_2$ is expected to increase by about 10 mmHg, while $PO_2$ is expected to decrease by 40 mmHg. During REM sleep, oxygen desaturation is almost always greater than in NREM sleep because apneic episodes are generally longer in this sleep stage.

The changes in blood gases are in part responsible for the autonomic nervous system changes that in turn lead to changes in the cardiovascular system.

*Cardiovascular consequences*

The apneic episodes set the stage for marked and complex changes in autonomic nervous system function. These changes are related to hypoxemia and hypercapnia, which may lead to both changes in sympathetic function and parasympathetic function, and to intrathoracic pressure changes which may change parasympathetic function and directly affect cardiovascular function. These form the framework that results in the acute cardiovascular changes seen in OSAS.

*Blood pressure*

In OSAS patients, there is an increase in sympathetic activity during sleep, which may explain the *arterial hypertension* that develops during sleep.[29] In normal people, blood pressure 'dips' during sleep, while in these patients, the pressure may not 'dip'.[30] A contributor to the arterial hypertension may be an increase in heart rate that occurs during the post-apnea ventilation phase, which could increase cardiac output. Hypoxia and hypercapnia may result in pulmonary arterial constriction that may ultimately lead to *pulmonary hypertension*[31-34] (see below). Because the *cerebral circulation vasodilates* in response to hypercapnia or hypoxemia, it is likely that cerebral vascular pressures and blood flow may change substantially during the apneic episodes.[35,36]

*Heart rate and rhythm*

Very common findings in patients with episodes of obstructive sleep apnea are episodes of bradycardia and tachycardia (see Fig. 5). The cause of these changes in heart rate is probably related to changes in autonomic nervous system activity. It is likely that the hypoxemia results in increases in sympathetic tone, while the negative intrathoracic pressure results in increased parasympathetic tone during the actual apneic episode. Thus, during apnea, and particularly at the end of apnea, the effect on parasympathetic tone causing bradycardia outweighs the sympathetic tone which would cause tachycardia. The release of the obstruction probably reduces the parasympathetic tone resulting in the tachycardic phase. Cardiac arrhythmias are also much more common in patients with apnea,[37] and they appear to be related to hypoxemia as well. The most severe forms of bradycardia that occur during episodes of apnea are related to heart block. This may result in profound brady-arrhythmias or even asystole.[38,39]

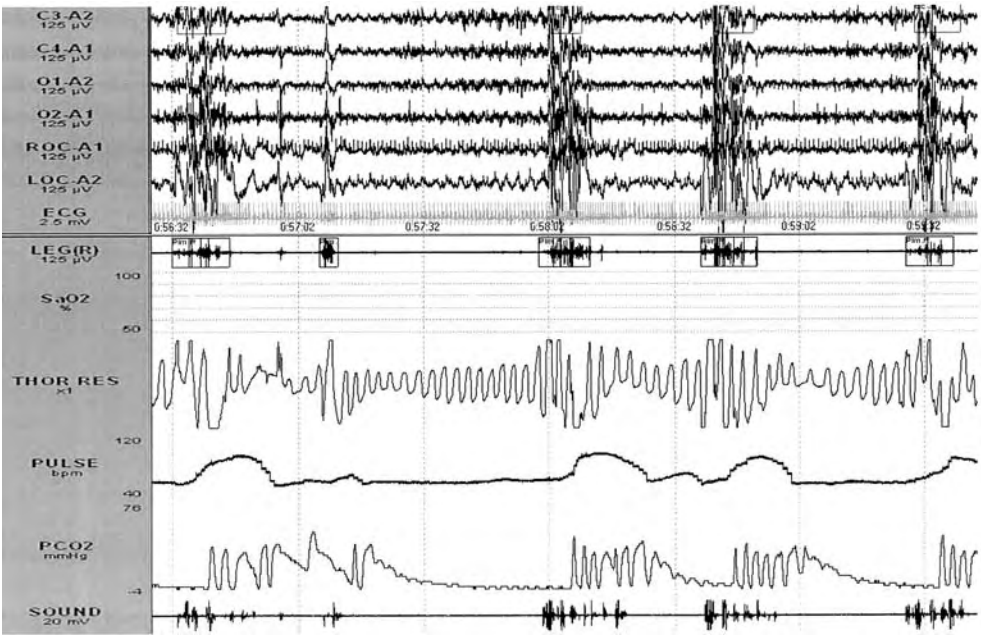


*Fig. 5.* A compressed polysomnographic trace in a patient with sleep apnea showing arousals in the EEG channels, repetitive hypoxemia, breathing effort (thor res), tachy-bradycardiac rhythm, airflow ($PCO_2$), and snoring sound.

*Cardiovascular function*

The oscillations in cardiac output, blood pressure, autonomic nervous system tone, etc., may explain the development of myocardial ischemia or congestive heart failure in patients with OSAS who already have a compromised cardiovascular system. Thus, patients with heart failure who also have OSAS may have dramatic improvement in their heart failure when treated with nasal continuous positive airway pressure.[6,40,41]

*Arousals causing sleep disruption*

One of the hallmarks of sleep breathing disorders is arousal.[24] Increased arousals are found in the entire spectrum of sleep breathing disorders, from the mildest upper airway resistance syndrome to the most severe. In OSAS, arousals play an important role in re-establishing ventilation. As reviewed above, with arousal there is an increase in motor activity to the upper airway muscles, re-establishing airflow. In some sleep breathing disorders, *e.g.*, Cheyne-Stokes respiration and heart failure, the arousals may not have the same role, but instead may simply be related to the respiratory effort found during the peak of hyperpnea.

The very large number of arousals that patients with OSAS have causes severe sleep fragmentation and unstable sleep. Thus, there is an increase in the

amount of stage 1 sleep, which is a transition state between wakefulness and sleep, and which is an index of sleep instability. These patients typically also have markedly reduced or absent slow wave sleep and may have a reduction in REM sleep. In upper airway resistance syndrome,[3] the only finding may simply be an increase in the number of arousals with fairly normal sleep architecture. In patients with severe sleep apnea, sleep architecture could be grossly abnormal.

## Pathophysiological mechanisms in the development of obesity hypoventilation syndrome

The key clinical and diagnostic finding in obesity hypoventilation syndrome (OHS) compared to obstructive sleep apnea/hypopnea syndrome is the presence of awake respiratory failure.[5,39,42,43] It is believed that blunted chemical drives to breathe (hypoxemia and hypercapnia) play an important role in the development of the respiratory failure. With successful treatment, such as weight loss, the drives to breathe may normalize. The hypoxemia and hypercapnia result in increased pulmonary artery pressure and might lead to cor pulmonale, resulting in peripheral edema. The hypoxemia also leads to an increased production of erythropoietin by the kidney, which in turn increases blood cell production. Thus, patients with OHS will have polycythemia. It is believed that pre-existing daytime hypoxemia may play an important role in the development of this syndrome. The clinical features of OHS were beautifully described in 1956.[5]

## Pathophysiological clinical consequences of obstructive sleep apnea syndrome

As mentioned above, patients with obstructive sleep breathing disorders may develop hypoxemia, hypercapnia, and abnormalities of autonomic nervous system function. As a result of these changes, the following may result.

### *Cardiovascular morbidity*

It has been shown that the increased sympathetic nerve activity that occurs in sleep apnea patients when they are asleep can persist into the daytime.[29] It has been shown in several studies that OSAS is an independent risk factor for the development of arterial hypertension, and the greater the apnea/hypopnea index, the greater the risk of having arterial hypertension.[44-47] Studies also suggest that there may be increased incidence of strokes[48] and ischemic heart disease[40,41,49-51] in patients with sleep apnea, but there are very few studies that have examined these other conditions in these patients.

*Neuropsychiatric morbidity*

Daytime sleepiness and other manifestations of central nervous system dysfunction are the most common presenting complaints of patients with sleep breathing disorders. Patients may present with sleepiness,[52] impaired cognitive function,[53,54] and neuropsychiatric symptoms.[55,56] It is widely believed that it is the sleep fragmentation secondary to the arousals that is the main contributor. For some of the more severe central nervous system dysfunctions, *e.g.*, impaired cognitive executive function, hypoxemia may also be playing a role.

*Obesity hypoventilation syndrome*

The most severely affected patients with sleep breathing disorders are those who ultimately develop obesity hypoventilation syndrome.[5] These patients, who are morbidly obese, ultimately develop both daytime hypoventilation, with an increase in arterial $PCO_2$ and $PO_2$, as well as nocturnal hypoventilation and severe sleep hypoxemia, whereas a typical patient with obstructive sleep apnea/hypopnea has normal control of breathing. These patients have blunted drives to both hypoxia and hypercapnia, which may play a role in the development of their continuous daytime and nighttime hypoventilation. It has been suggested that hypoxemia may ultimately lead to the development of this hypoventilation syndrome. It has also been shown that if patients lose sufficient weight, or are treated with ventilatory assistance, this severe syndrome may resolve entirely. There is said to be a high mortality in this group.[4]

## Pathophysiological basis of the obstructive sleep breathing disorders

In obstructive sleep breathing disorders, the clinical features tend to be directly linked to the pathophysiological mechanisms (Fig. 6). Understanding the pathophysiological mechanisms reviewed above is thus an important first step in understanding the many presentations of these disorders.

There is a very broad spectrum of sleep breathing disorders. These range from asymptomatic snoring to upper airway resistance syndrome, to OSAS, and to OHS. All these disorders have in common increased upper airway resistance during sleep.

With *asymptomatic snoring*, it is believed that gas exchange and cardiovascular function are maintained at normal levels, although it has been speculated that there may be long-term cardiovascular sequelae with snoring.

Patients with *upper airway resistance syndrome* may have an apnea/hypopnea index within normal limits, but may demonstrate increased arousals during sleep, snorts, and daytime sleepiness.

Patients with *obstructive sleep apnea/hypopnea syndrome* have repetitive episodes of apnea or hypopnea, abnormalities in gas exchange and cardiovascular function, abnormal sleep structure, and excessive daytime sleepiness.

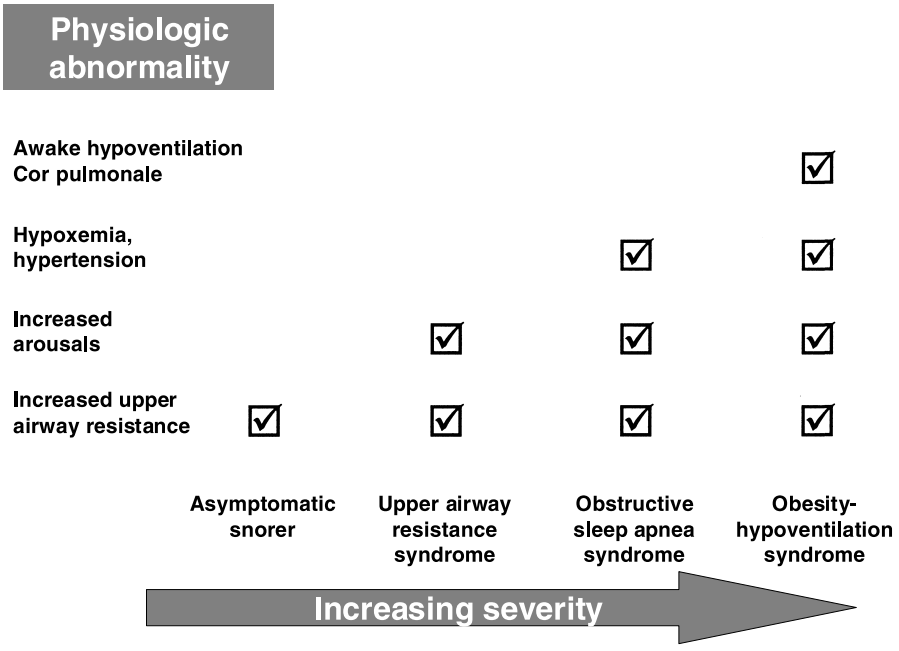


*Fig. 6.* The spectrum of obstructive sleep breathing disorders ranges from the least severe, asymptomatic snoring to the most severe, obesity hypoventilation syndrome. The more severe syndromes are associated with more physiological abnormalities.

Patients with *obesity hypoventilation syndrome* (or Pickwickian syndrome) develop hypoventilation as indicated by increased $PCO_2$ both during the day and night, and the consequences of the respiratory failure, mainly cor pulmonale and polycythemia.

Each type of sleep disordered breathing abnormality just mentioned is more severe than the one preceding it, with more physiological abnormalities and resultant clinical consequences. An understanding of the pathophysiological mechanisms establishes the rationale for treatment.

## Conclusions

The obstructive sleep breathing disorders make up a spectrum of syndromes, which range from the asymptomatic snorer, to upper airway resistance syndrome, to OSAS, and to OHS (see Fig. 6). At one extreme, people with the mildest problem, upper airway resistance syndrome, probably do not have an increased risk of death. At the other extreme, patients with OHS are at risk because of their respiratory failure and probably have an increased risk of death. Understanding the pathophysiology of sleep-disordered breathing develops a framework to help understand the syndromes. What binds these syndromes

together is the increased upper airway resistance during sleep, and it is relief of this upper airway resistance that constitutes the main goal of therapy. The various therapeutic modalities available in sleep apnea are reviewed in other chapters in this volume.

## Acknowledgment

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# OBSTRUCTIVE SLEEP APNEA AND CARDIOVASCULAR DISEASE

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**Hemodynamic and respiratory changes during normal sleep** (Figs. 1 and 2)

Normal sleep is associated with a decrease in both tidal volume and respiratory frequency, as well as in heart rate and arterial pressure. These effects are constant during non-REM sleep and are proportional to its depth. However, in REM sleep, the cardiovascular and respiratory activity are not steadily depressed,

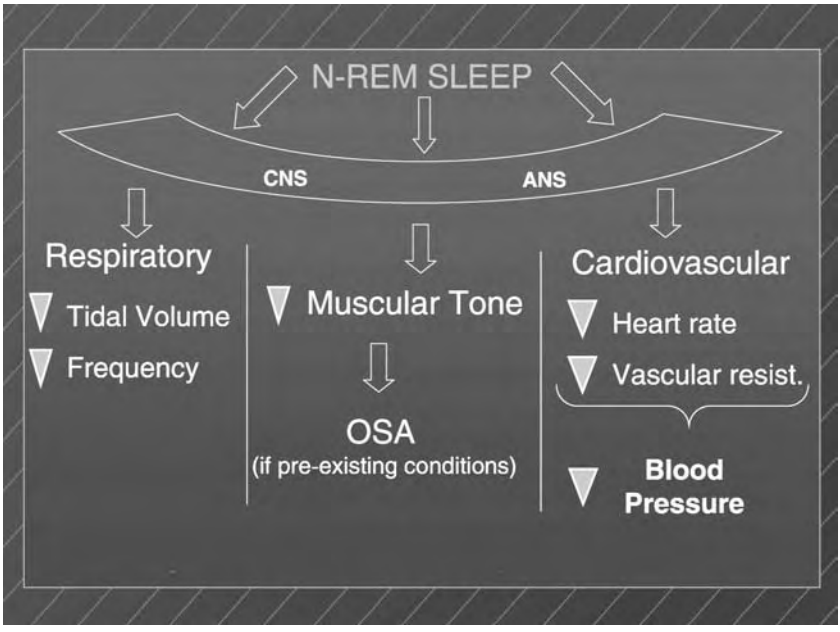


*Fig. 1.*

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*Surgery for Snoring and Obstructive Sleep Apnea Syndrome, pp. 63–71*
*edited by M. Fabiani*

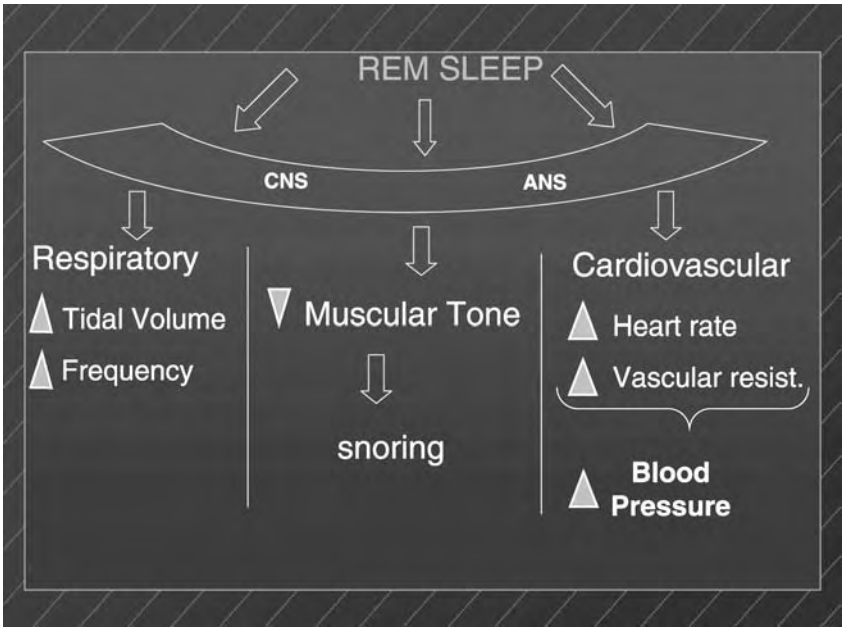
REM SLEEP
CNS
ANS
Respiratory
Tidal Volume
Frequency
Muscular Tone
snoring
Cardiovascular
Heart rate
Vascular resist.
Blood Pressure

*Fig. 2.*

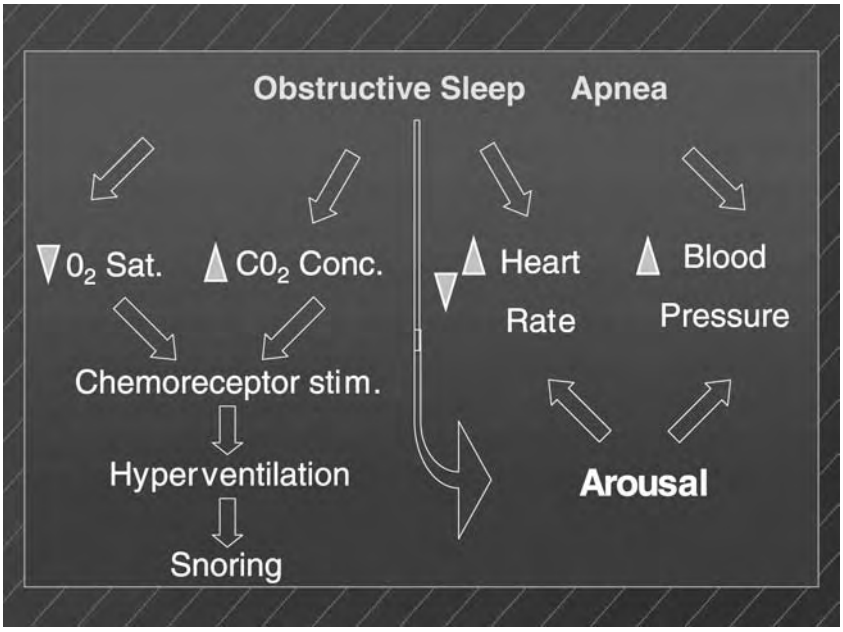
Obstructive Sleep Apnea
$0_2$ Sat.
$C0_2$ Conc.
Heart Rate
Blood Pressure
Chemoreceptor stim.
Hyperventilation
Snoring
Arousal

*Fig. 3.*

but are characterized by extreme variability, and an irregular rise in breathing. The highest and lowest heart rates and arterial pressure values are usually observed during this stage.

The hemodynamic changes observed during sleep are related to variations in sympathetic or/and parasympathetic tone. The decrease in sympathetic output, constantly present in non-REM sleep, produces a reduction in arterial pressure by two different mechanisms: a reduction in cardiac output, much more frequent in younger subjects, through an increased vagal tone; and a reduction in vascular resistance with constant cardiac output, especially in older individuals, through a decrease in sympathetic activity (Fig. 3). However, during REM sleep, there is an increase in sympathetic activity leading to large fluctuations in heart rate and arterial pressure. The respiratory pattern seems to depend, above all, upon changes in $O_2$ saturation and $CO_2$ concentration in the blood.[1-7]

**Hemodynamic and respiratory changes associated with obstructive sleep apnea** (Fig. 4)

Obstructive sleep apnea (OSA), of which snoring is a sign, is characterized by sporadic interruptions in the air flow due to occlusion of the upper airways, caused by a reduction in pharyngeal muscular tone which acts on the already existing anatomical narrowness of the upper airways. Due to the airway occlusion, hypoxemia always occurs and hypercapnia often. These events are self-

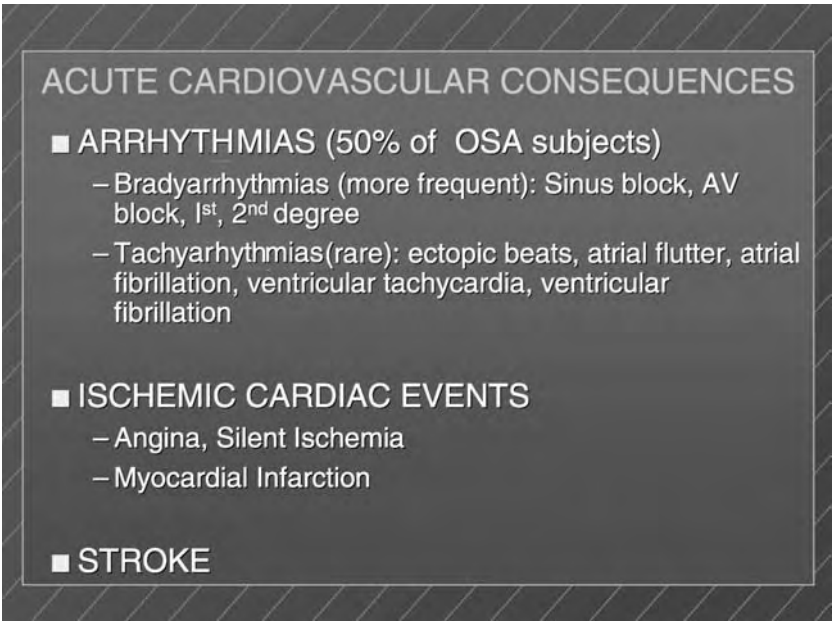


*Fig. 4.*

limiting, because the chemoreceptor stimulation, together with mechanical stimuli from the upper airways, determines a sudden increase in the tone of the dilatory muscles of the upper airways until permeability has recovered. The chemoreceptor stimulation also causes hyperventilation, and consequently intense snoring.[8] The recovery in breathing often coincides with a short awakening, of which the patient is normally unaware, and sometimes with definite awakening. OSA is accompanied by large oscillations in heart rate, pulmonary and systemic pressure, and in right and left ventricular stroke volume. These changes occur in association with hypoxemia, an increase in pleural and lung volume, and disruption of sleep. Sympathetic hyperactivity is usually also seen with the hemodynamic modifications.

*Heart rate changes*

Patients with OSA experience repetitive cardiac slowing down and acceleration:

The slowest heart rate most commonly occurs at the onset of apnea, when the air flow ceases. During apnea, the heart rate accelerates, probably reflecting chemostimulation. At the termination of apnea, the heart rate accelerates even more, peaking a few seconds after the release of the airway obstruction.

A second pattern, which appears to be less common, is when the heart rate slows down, not only at the onset of apnea, but also until its termination.

It is unknown what determines whether a patient displays slowing down or acceleration at the termination of apnea. Sleep stage, degree of oxygen desaturation, and individual differences, may be important variables.[9]

*Arterial pressure/cardiac output*

At the termination of apnea, an abrupt surge of arterial pressure is commonly seen. The two factors proven to be effective in such event are oxygen desaturation and the sudden disruption of sleep. Both these factors seem to operate through sympathetic activation. A number of lines of evidence support the importance of hypoxic chemostimulation and of holding the breath in this acute response. However, whether it is caused by arousal or chemostimulation, the change in pressure must reflect an increase in either cardiac output or systemic vascular resistance, or both. The change in cardiac output appears to be mainly dependent on an increase in heart rate, rather than on left ventricular stroke.[10-12]

## Cardiovascular morbidity associated with obstructive sleep apnea

From the above, a causal role for OSA in cardiovascular disease would seem plausible. Extreme oscillations in heart rate, arterial pressure and stroke volume, all possibly occurring in association with a deep decrease in arterial oxy-

gen saturation, would logically seem to increase the risk of morbid cardiovascular events.[13]

*Acute cardiovascular consequences* (Fig. 5)

*Arrythmias*

As described above, the heart rate oscillates in association with sleep apnea. Superimposed on these oscillations, atrial and ventricular arrythmias have both been observed in almost 50% of subjects. Bradyarrhythmias (sinus arrest, atrioventricular blocks) are more common, while severe tachyarrhythmias are rare.[14,15]

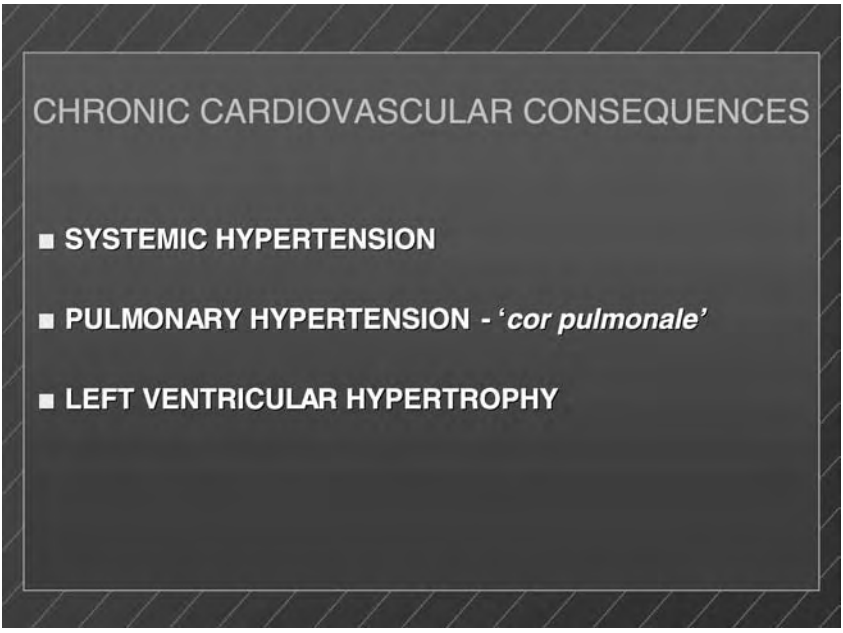


*Fig. 5.*

*Myocardial infarction*

The extreme oscillations in arterial pressure and heart rate, occurring during OSA, have indicated their causal role in myocardial ischemia. Despite the convincing pathophysiological basis, there is little evidence to support OSA contributing to myocardial infarction. A large study from Scandinavia reported an increased odds ratio (OR) for angina in subjects reporting regular snoring.[16] Another community-based study performed in Mexican-American subjects found an increased OR for myocardial infarction.[17] The findings of two Australian studies were also consistent with a small elevation in cardiovascular risk attributable to sleep apnea.[18,19] The electrocardiographic monitoring of sleep apnea patients also shows many episodes of silent ischemia. However, none of these studies are conclusive, owing to the somewhat confounding factors in patient

selection, such as obesity, pulmonary vascular congestion, periodic breathing, associated medications, etc. Therefore, should the results of the Sleep Heart Health Study[20] be unavailable, the data on myocardial infarction and OSA are not definitive.

*Stroke*

Several studies using Doppler techniques have shown a decrease in middle cerebral artery flow at the end of episodes of sleep apnea.[21,22] Nevertheless, there is no clear evidence to show an increased risk of stroke attributable to sleep apnea. The majority of studies, showing a relationship between stroke and OSA, examines the prevalence of sleep-disordered breathing in patients who have recently suffered a central stroke. The positive correlation observed could certainly indicate a causal relationship between sleep apnea and stroke, but the opposite cannot be excluded either.

*Chronic cardiovascular consequences* (Fig. 6)

*Systemic hypertension*

Epidemiological data, as well as animal experiments, strongly support a causal role for OSA in the development of systemic hypertension in susceptible individuals.[23] It has been shown that sleep apnea, defined as more than 20 desaturations per hour of sleep, brings with it a relative risk of hypertension of 2.1 times.[24] Another study demonstrated that subjects with an apnea index greater than five

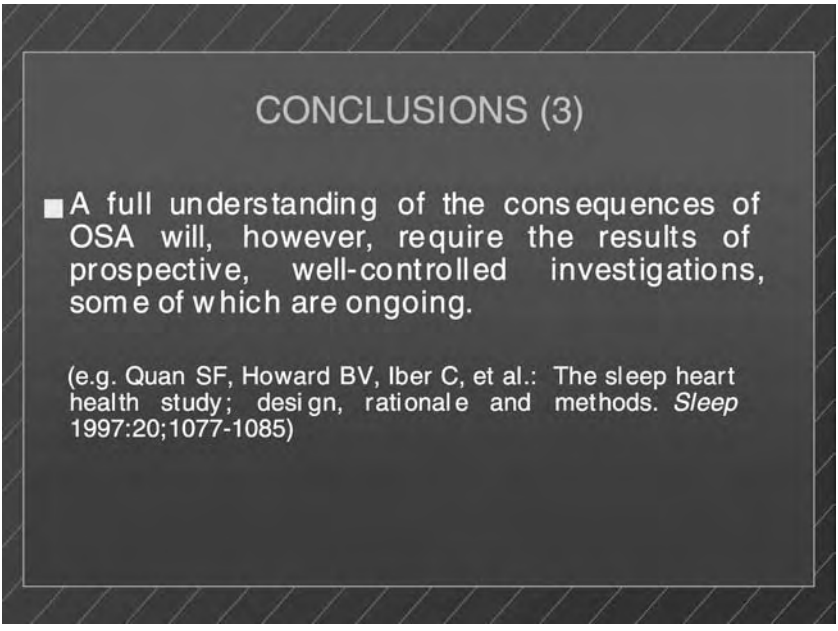


*Fig. 6.*

events per hour of sleep, had significantly higher systemic pressure than individuals who snored but did not suffer from apnea, or individuals who did not snore.[25] The mechanism by which sleep apnea causes hypertension has been identified in the causal link between intermittent hypoxemia and sympathetic hyperactivity. However, treatment with nasal continuous positive airways pressure (CPAP) results in a decrease in resting sympathetic tone and sometimes in arterial pressure.[26] During sleep, the arterial hypertension in OSA patients does not decrease at the same level as that in non-apneic subjects.

*Pulmonary hypertension*

Pulmonary hypertension is a frequent finding in subjects suffering from OSA, as is, as a direct consequence, so-called right heart failure. Experimental data in both animals and humans support the causal role of hypoxia in developing pulmonary hypertension and right ventricular hypertrophy.[27] Nevertheless, the connection between OSA and chronic pulmonary hypertension has been called into question by a study reporting a case series in which only OSA patients with hypoxemia while awake developed the clinical features of cor pulmonale.[28] The need for waking hypoxemia as a requirement for right heart failure is not contrary to the above-mentioned opinion, due to the obvious more intense effect of chronic hypoxemia versus the intermittent. From the data that are currently available, OSA can be seen to be a cause of a mild elevation in pulmonary artery pressure, but not as the sole cause of severe pulmonary hypertension.[29]

*Left ventricular hypertrophy*

Hypertensive individuals who lack normal nocturnal arterial pressure decline (so-called 'non-dippers') have a greater left ventricular mass than subjects with the same waking arterial pressure, but whose arterial pressure decreases by more than 10% during sleep (so-called 'dippers').[30] Since the arterial pressure of sleep apnea patients fails to decrease during sleep, these subjects would seem to be at greater risk for the development of left ventricular hypertrophy. Unfortunately, studies investigating the independent effect of sleep apnea on left ventricular mass arrived at opposing conclusions.[31,32] However, the study that found no effect had many 'dippers' among its OSA patients. It seems reasonable that left ventricular hypertrophy is more dependent on the total pressure load than on sleep apnea, among all the other factors involved.

## Conclusions

Patients with OSA experience repetitive nocturnal oscillations of their heart rate, pulmonary and systemic arterial pressure, and cardiac function. These cardiovascular changes are associated with a decrease in oxygen saturation, sometimes a rise in carbon dioxide concentration, and a variation in lung volume. The patients are frequently aroused from sleep.

Although a causal connection between OSA and acute cardiovascular morbidity has not yet been established, it seems likely that these dramatic hemodynamic changes during sleep may contribute to acute cardiovascular events in susceptible individuals. Furthermore, many data show that OSA contributes to chronic cardiovascular diseases, such as systemic and pulmonary hypertension and left ventricular hypertrophy.

However, to fully understand the consequences of OSA will require the results of prospective, well-controlled investigations, some of which are ongoing.

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# NASAL OBSTRUCTION AND OBSTRUCTIVE SLEEP APNEA SYNDROME

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## Introduction

Nasal obstruction (NO) is certainly one of the most common and recurrent symptoms in the clinical practice of otolaryngology. Over the past decades, it has been taken into consideration on various occasions to identify pathologies responsible for snoring and obstructive sleep apnea syndrome (OSAS), even when this pathological condition also includes a number of other causes that interact among themselves. In fact, anatomical-functional factors, such as the cardiopulmonary system, base of the tongue, tonicity of the pharyngeal muscles and the soft palate, all considerably influence the identification of this syndrome. However, many have accepted that nasal obstructive pathologies can represent the starting point of the sequence of events consisting of obstruction-snoring-apnea and further metabolic disorders that, above all, suggest that the nose should be treated first.

It seemed a good idea to once more briefly examine the steps provided by various data in the literature that indicate how the study and solving of nasal problems is an important initial factor in the solution of this important pathological situation.

In his publication *Shut your mouth and save your life*, Catlin,[1] a 19th century American jurist, observed how, in the Indian-American population, correct nasal breathing was taught to small children. Later on, Hill in 1889,[2] Carpenter[3] and Cline in 1892[4] indicated the links between nasal obstruction, sleeping problems, and nighttime apnea. More recently, during the 1950s, obesity was associated with these problems, the typical patient with OSAS being indicated in the Pickwick syndrome (Siecker, 1955[5]; Burwell, 1956[6]). During the years between the 1960s and the 1980s, interest in these clinical situations moved to the fields of neurology, cardiology, and pneumatology, with studies that examined the different and complex mechanisms of extranasal pathologies.[7-9]

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However, Cottle[10] deserves recognition for having given back to the nose its leading role in the etiological moment of snoring and OSAS.

The 1980s were extremely rich in publications concerning the relationship between nasal obstruction (anatomical structure and mucous membrane) and breathing problems while sleeping.[11-15] Sulsenti and Palma[16] describe how nasal surgery should be considered a necessary requirement before uvular-palate-plastic surgery. However, we must always remember that, however important the role played by the nose in snoring problems and OSAS may be, we cannot set aside a global vision of the nasal-palate-pharynx. In fact, nasal obstruction determines the upper airway resistance syndrome (UARS) that causes the collapse of the oral and hypopharyngeal walls.

Biomechanical studies have already widely underlined the importance of relationship between the area used for inspiration and resistance to flow: the reduction of this interaction causes the progression of snoring > UARS > OSAS. There are in fact three resistance sectors in which this relationship is strongly stressed: the frontal area of the nose (the nasal valve), the palate, and the base of the tongue.[17] It is evident that, in the diversification of resistance areas (nose) and collapsible areas (pharynx), we must also pay attention to the first of these; in fact, although epidemiological data state that nasal obstruction is present in about 80% of patients presenting for OSAS surgery, it has in fact never been diagnosed alone, while, for example, it is present in 35% of cases associated with pathologies of the velum and base of the tongue; these data indicate that an isolated obstructive nasal syndrome does not exist in the identification of OSAS, and that therefore there cannot be isolated nasal surgery in the therapeutic protocol for OSAS.

When considering the particular nasal anatomical-physiological characteristics, we must understand which segments are responsible for the obstruction in order to set out the next therapeutic protocol for nasal surgery. Nasal obstruction causes oscillation of the palate and consequent snoring by means of two mechanisms: an increase in flow turbulence and breathing through the mouth which, in turn, determines relaxation of the genioglossus and geniohyoid muscles. There is still debate regarding the dilemma of whether nasal surgery acts positively on snoring pathologies and also on OSAS, even though, taking into account previous considerations, we do not think this to be the case. In 1991, Fairbanks[18] published the results of a study on 47 patients affected by simple snoring, who had undergone nasal surgery: of these, 80% improved considerably; but the problem remains: is the sequence nasal occlusion > nasal resistance > negative pharyngeal pressure-failure of the respiratory tract a valid one? In other words, does nasal obstruction cause OSAS? Blakley and Mahowald[19] refute this, correctly stating that the increase in nasal resistance does not appear to be the main factor in the development of apnea syndrome, but simply a co-factor.

## Physiological anatomy of the nasal region

The 'external' nose should simply be considered to be composed of nasal bones, nasal septum, and upper and lower cartilages; in the interior of the nose, there are the nasal septum and turbinates. In fact, in respiratory obstruction pathologies, above all, we must take into account the areas showing anatomical contraction. These are represented by the external naris (columella and narial edge), internal naris or nasal valve, and extreme naris (choana). The nasal valve consists of the caudal edge of the upper cartilages and the corresponding projection on the septum and the base of the nasal fossae, where it meets the insertion of the head of the inferior turbinate. Finally, the extreme valve is represented by the opening of the choanae and can be altered by thickening of the septum and by hypertrophy of the tail end of the inferior turbinate.

Considering that the area of the nasal valve is the region that limits the flow of the entire higher respiratory tract, even modest anatomical alterations in this area can result in important consequences for snoring pathologies. Applying Poiseulle's law in balance with linear and turbulent nasal flow, the most important factor regarding resistance to the flow (and therefore to nasal obstruction) is the radium of the nasal valve raised to the fourth power. With extreme inspiratory efforts, this segment collapses due to the pressure decrease that takes place within the nasal valve. This more often takes place in mesorhine or leporine patients and in elderly patients because of the physiological lassitude of the tissues; the platyrrhine type is not in fact susceptible to this kind of failure, because of the opposition applied by the dilatation side muscle (*Dilator naris*) during deep inspiration.[20] Apart from these anatomical causes, obstruction – due to the characteristic histology of the nasal mucous membrane and its innervation - can be caused by hyperactivity of the parasympathetic system or by a lack of activity of the sympathetic system (dilatation of the capillaries and vein congestion).

Resistance to flow is important in nasal physiology since its turbulence, which optimizes the contact of the air breathed in with the mucous membrane, facilitates the conditioning of the air itself. To sum up, understanding the nasal flow is complicated, and the clinician is often too accustomed to patients complaining of a respiratory obstruction, while clinical examination of the nose reveals a wide cavity. In fact, the feeling of an obstruction can occur despite the presence of a wide nasal valve (*e.g.*, due to turbinectomy), because of the excessive turbulence of the flow; the same turbulence that is responsible for the atrophic changes in the nasal septum or metaplasia of the mucous membrane in the head of the turbinate.

The feeling of a 'free nose' is also connected with the anatomical-physiological relationships in the entire higher respiratory tract; in fact, resistance must remain within certain limits in order to maintain normal breathing. If resistance is too high or too low, the patient will experience a feeling of obstruction. Conservation of the resistance during nasal breathing contributes to

the optimal opening of the alveolus during breathing, with positive effects on the gaseous exchange.

## Clinical evaluation of nasal obstruction

Case history and clinical evaluation should effectively orientate the specialist faced with symptoms of nasal obstruction; length of time since onset and symptoms, factors that alleviate the symptoms, single or bilateral characteristics, constant or intermittent obstruction. Other symptoms will also be of interest, such as the presence, characteristics, smell of the rhinorrhea, history of epistaxis, nose pain or headaches, eye symptoms, otalgia or autophony, case history of respiratory illnesses (asthma, sinusitis), frequent use of medicines or alcohol, tobacco or drugs. We believe that, as in many other clinical situations, a good case history can lead to a correct diagnosis. For example, bilateralism of symptoms of varying seriousness can indicate mucous membrane alterations, while a constant obstruction might lead the specialist to think of a probable anatomical or, in any event, structural cause. Pathologies concerning the mucous membrane are usually bilateral, while anatomical problems can be unilateral or bilateral, and should the obstruction be linked to the seasons, allergic causes would of course be considered. Clear and widespread rhinorrhea is normally caused by a vasomotor rhinological pathology, but this does not exclude cerebral spinal fluid leakage.

The external shape of the nose is easy to examine in order to determine its dimensions and any possible link to deformation or deviation of the septum. The presence of scabs or situations similar to eczematous skin problems are a sign of frequent cleaning of the nose or, on the other hand, of a lack of hygiene. It is also important to observe the point of the nose, which may show excessive drooping, and the depth and wideness of the side cartilages, which may work as a valve during inspiration.[21]

The face should be examined to underline any possible muscular paresis, and the sinuses and paranasal structure should be evaluated for any possible tenderness.

This is followed by examination of the eyeballs, ears, and lateral cervical lymph nodes, after which anterior and posterior rhinoscopy is carried out. At this time, the degree of congestion of the mucous membrane, edema, type of rhinorrhea, and color of the mucous membrane is also evaluated. Administration of a topical vasoconstrictor enables more accurate examination of the anatomy of the nasal septum and turbinates; endoscopy with flexible and rigid fibers, or curved ones, completes the examination. Endoscopy enables more detailed evaluation of the turbinates, meatus, back of the septum, and rhinopharynx.

Clinical examination of secretions and nasal cytology helps the specialist to come to a diagnosis (rhino-liquorrea, allergies). Rhinomanometry and acoustic rhinometry are used to evaluate the amount of nasal obstruction present; other

useful elements are a complete blood test, (including VES, calcemia – high in the presence of sarcoids – test for mycetes, tests for TBC and syphilis).

Modern radiological studies should only include CT scan of the nose and nasal sinuses in axial and coronal projections; in some cases, MRI can supply further information on soft tissue components. Finally, bioptic tests must be included when an unusual inflammatory process (Wegener's disease) is suspected.

## Specific etiologies in nasal obstruction

### *Anatomical anomalies*

The most usual anatomical causes of nasal obstruction include deviation of the septum and concha bullosa, and alterations of the nasal valve. Less frequent are perforations of the septum or choanal atresia.

*Deviation of the septum*

This is certainly one of the commonest causes. In these cases, the history of traumatic nasal events, which could be of congenital origin, can lead to a diagnosis: a trauma can dislocate the nasal bones, upper cartilages or septum, or various elements at the same time. At the same time, there may be a history of sinus phlogosis caused by alteration of the sinus mucous draining following obstruction of the openings, and alteration in the flow with local turbulent currents and consequent histological changes in the mucous membrane. The deviation may include the cartilage septum, bone, or both; sometimes, rather than being deviated, the septum is enlarged, at the cost of the breathing space.

However, deviation of the back septum (vomer and perpendicular lamina of the ethmoid) is less frequent. When the nasal valve is tightened in a certain area, thickening of the mucous membrane, scabs, atrophic modifications of the mucous membrane, and the local turbulent currents alter the flow that is already compromised even more. Naturally, the protocol for surgery anticipates functional correction of the septum. However, it should be borne in mind that functional nasal surgery not only affects the septum and turbinate, but also the nasal valve from an overall point of view, from any possible asymmetrical shapes with various opening widths to the vascular and muscular dynamic component.

In fact, nasal physiology discourages the old submucous resection operation, confirming the need to keep an average structure (septum) in order to maintain a correct nasal cycle.[22,23]

Considering that the aerodynamic importance of the lower level is greater than that of the higher, surgery of the turbinates must be part of the total balance of the nasal physiology. Let us not forget that, in the absence of a solid

median structure, the turbinates themselves would maintain a 'pathological' hypertrophy that would lead to nasal obstruction.

*Hypertrophy of the turbinates*

When there is primary or secondary hypertrophy of the turbinates, the chosen medical or surgical treatment will depend on the primary alteration of the mucous membrane (epithelial) or anatomical structure. Reversible mucous membrane pathologies frequently respond to infranasal steroids, and sodium neocromile can also help in patients who are really allergic; however, changes in the mucous membrane often do not respond to medical therapy, and various decongesting techniques can and must reduce the volume of the turbinates: cryotherapy, electrocautery, submucous membrane steroid depot injections, Coblator R with radiofrequency, or simple surgical techniques for sectioning, are often used.

We must always remember that resection of the submucous membrane must find a balance between reduction of volume, increasing the air space, and the corresponding risk of creating turbulent air streams.

*Perforation of the nasal septum*

Perforation of the septum can sometimes be present without symptoms, but it is often accompanied by scabs or bleeding and noises being made while breathing. Even though the passage of air through the nose is increased by the perforation, the creation of turbulent flows causes a feeling of nasal obstruction, and the same adjacent turbinate may become hypertrophic, modifying the flow of the lamina even further. Small perforations (up to 1 cm) can be treated with strips of mucoperichondrial and labiobucconasal rotation flaps; perichondrium-periostrium grafts (ears) can increase the percentage of success.[24] Larger perforations require access through an alar base incision or via external rhinoplastic surgery, which allows a better surgical view. It is important to note that perforations caused by the taking of cocaine are far more difficult to close, because the nasal septum has often been completely destroyed and because of the presence of 'cutting' substances with a sharp vasoconstrictive effect.

In some patients, insertion of a silicone nasal button under local anesthesia may alleviate the symptoms, especially in medium to large perforations.

*Alterations in the nasal valve*

Alterations in the nasal valve occur when the higher part of the nose collapses during inspiration; in these cases, the lateral tissues are unable to combat the internal negative pressure generated by the Venturi effect and, during inspiration, stop the incoming air from entering. This typically happens at the joint between the caudal margin of the upper cartilage and the nasal septum (the nasal valvular area): this may occur because of a structural narrowing associated with insufficient cartilage support in the external nasal tissue. However, the problem is often iatrogenic, caused by excessive removal of cartilage at the

intercartilage joint (the joining of the higher and lower cartilages), which is often the consequence of plastic surgery.

For aesthetic reasons, a number of surgeons cut off the lateral crus of the lower cartilage excessively, thus creating deformity and failure of the valve.[25] This deformity can also occur with age, when the nasal and supranasal tissues become weaker because of the loss of elastic support. Valve failure is easily identifiable by deep intakes of breath with one nostril obstructed; the patient is immediately more comfortable with the introduction of a nasal speculum or lateral traction of the skin in the jaw area.

Surgical treatment is used for correction of the nasal valve, with plastic surgery of the septum being used to insert cartilage taken from the auricular concha or septum cartilage when this is available. When the nose is tight, Weir's approach, which suggests surgery based on widening of the pyriform opening using basic osteotomy, can prove useful;[25] however, the objective of all surgical protocols is to increase the area of the nasal valve, because of the well-known relationship with the fourth power of the radius.

*Pathologies of the mucous membrane*

Whatever the prominent etiology might be, the final anatomical-pathological situation consists of hypertrophy of the inferior turbinate.

The inferior turbinates undergo numerous variations during the day due to the nasal cycle, which consists of a physiological and alternated increase and reduction of nasal resistance every three to four hours. Once hypertrophy of the head of the inferior turbinate has set in, it causes greater resistance to the nasal flow at an immediate postvalvular level; the most common pathological causes of hypertrophy of the inferior turbinate are represented by compensating hypertrophy of the inferior turbinate contrasting the concavity of the deviated septum, and the presence of allergic, pseudoallergic, vasomotor and hypertrophic rhinitis.

In its long-term development, allergic rhinitis is not only associated with hypertrophy of the turbinates, but can also cause nasal polyposis or bronchial asthma. This explains the frequent association of nasal allergies with rhinopathy and/or OSAS.

Pseudo-allergic rhinitis is based on anatomical, physiological, and clinical factors, and is stimulated by external (environment, UVA rays) or endogenous (endocrinopathy, stress) factors. Sluder's neuralgia and the corresponding parasympathetic vasodilative and secretory activity of the nasal mucous membrane are also a common cause.

Vasomotor rhinitis is found in various pathologies and is not always easy to deal with. It is probable that a neurovegetative dystonia occurs, which does not lead to the liberation of histamines and similar substances, but mainly affects the functional activity of the cavernous structures situated at the level of the middle, and especially the inferior, turbinate. In this case, as in pseudo-allergic

forms, a parasympathetic predominance is observed as well as the freeing of neurotransmitters, not only acetylcholine, although they are often correlated (especially VIP), whose activity determines vasodilatation and glandular hypersecretion. Very recently, much attention has been paid to the releasing, following various stimuli, of substance P which determines vasodilatation, an increase in vasal permeability, and glandular hypersecretion.[26]

This form of rhinitis is never accompanied by sneezing fits, nor are there exudative manifestations: the symptoms are simply a noncontinuous, intermittent, mono- or bilateral, nasal respiratory obstruction, sometimes alternating between the two nasal cavities. On examination of the nasal mucous membrane by means of frontal rhinoscopy, it usually appears congested and bruised. Cases in which congestion, and therefore nasal obstruction, is most evident normally evolve towards hypertrophy of the turbinates.

Simple hypertrophic rhinitis is particularly found in subjects who work in over-heated environments, in heavy eaters and drinkers, and in patients with endocrine dysfunction (hyperthyroidism, acromegaly).

Mucous membrane hypertrophy is often selectively localized at the base of the inferior turbinates, whose hypertrophy may in part obstruct the choana. From a histological point of view, hypertrophy appears to be considerable in many cases with especially high levels of serum mucous glandular structures, in other cases due to hyperplastic vascular structures, and in yet others due to the chronic bruised condition of the mucous chorion; because of the frequent overlapping of vasomotor phenomena, the obstruction may increase alternatively in the nasal cavities.[27]

Medicamentous rhinitis is a form of the illness developed due to the abuse of drops or decongesting nasal sprays containing sympathicomimetic substances (patients even use up to a box of the product per day). This causes contraction of the subepithelial precapillary sphincters, arteriolar vessels, and venous sinusoids. This initial vasoconstriction is followed by a secondary vasodilatation caused by the constricting mechanisms and hypoxia. An increase in the secretions from the muciparous glands and of the nasal obstruction, and a reduction of mucous clearance, will be seen.

## Discussion and conclusions

Considering that every obstructive nasal pathology requires medical treatment (for alterations in the mucous membrane) or specific surgery (for anatomical alterations), we should analyze the precise role of the nasal respiratory tract in the pathogenesis of OSAS. The correction of obstructions in the higher respiratory tract is still considered an important component in the therapeutic protocol for OSAS.[11,28,29] It is universally accepted that the correction of a nasal obstruction by modifying the septum and turbinates generally improves the symptoms in patients with OSAS.[15,30] Therefore, the correction of nasal ob-

structions is a crucial issue in treating OSAS. We have previously observed how nasal obstructions increase nasal resistance and lead to sleep with respiratory problems, including apnea, ipopnea, and snoring.[15]

Deformities of the septum may predispose patients to apneas and hypopnea.[31,32] In addition, phlogosis of the mucous membrane of the respiratory tract (rhinitis, sinusitis) can further intensify breathing problems during sleep. Clinical and experimental data prove that nasal phlogosis causes an increase in nasal resistance that can lead to OSAS.[33,34] Despite subjective findings, analysis of the published literature does not reveal any objective evidence of improvement of OSAS on the basis of polysomnographic findings.[35]

Therefore, the problem of the pathogenetic relationship between nasal obstruction, snoring pathologies, and OSAS remains unsolved, and the indications for the ENT specialist should be evaluated with extreme care in obstructive nasal pathologies, with regard to the various factors that should be investigated by a neurologist and a clinical doctor: in other words, is a specialist ENT examination capable of attributing a specific percentage of OSAS to respiratory nasal obstruction? When it is not only the nose that is responsible for apnea/OSAS, should its treatment be preceded by, or linked to, other medical or surgical treatments?

We believe that the analysis of pathologies found in ENT surgery for OSAS can answer the first question; in fact, epidemiological data state that, in 80% of cases, there is a nasal obstruction but that this obstruction is never present alone, but always in connection with pathologies of the pharynx (35%) or of the pharynx and the base of the tongue (35%).

Recently presented results after functional nasal surgery confirm these data;[36] in fact, despite an objective improvement (measured with rhinometry) in nasal resistance of over 90%, the problems linked to snoring only improved in 34% of cases; in addition, the level of night-time respiratory problems (RDI) and of $O_2$ saturation ($LSaO_2$) did not improve greatly.

However, the finding that appears positive in this connection is the reduction of continuous positive airway pressure (CPAP) levels after nasal surgery, which allows an increase in the number of patients who can tolerate CPAP itself. It must be mentioned that, even relief from nasal obstruction, allows the patient to sleep more comfortably, alleviating the inconvenience of fragmented sleep.[37] The data concerning RDI confirm that co-factors present in OSAS must lead to a different therapeutic attitude in which nasal surgery must assume a *primum movens* role; this will give the ENT specialist sufficient discretion to make better use of the surgical techniques available. This, in turn, will help to guide patients with OSAS towards their ultimate goal, that of recovery.

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# OBESITY AND OBSTRUCTIVE SLEEP APNEA SYNDROME

# WEIGHT-MANAGEMENT STRATEGIES FOR OBESITY IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA SYNDROME

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## Introduction

In the past, success in the treatment of obesity was measured by how rapidly weight was lost and the amount of weight lost.[1] Today, success should be measured by the ability to achieve and maintain a clinically helpful and significant weight loss and by the positive effects of weight loss on the comorbidities of obesity, such as diabetes mellitus type 2, hypertension, and dyslipidemia.

Weight-loss management strategies can be classified into three broad categories: basic treatment, pharmacotherapy, and surgical treatment.

## Basic treatment

All obese patients, whether or not they are candidates for pharmacotherapy or surgical treatment, should undergo basic treatment. This basic treatment should include counselling, caloric restriction, behavior therapy, and physical activity. The goal of any basic treatment program is to integrate positive eating and physical activity behaviors into the patient's life.

Many placebo-controlled studies have shown that such basic treatment can successfully yield a weight loss of approximately one pound per week in some patients, without the aid of pharmacotherapy or surgical treatment.[1,2] Nevertheless, patients often revert to their old behavior and regain weight. Therefore, a structured weight-maintenance program with indefinite, continual contact is also needed to help the patient sustain weight loss.

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*Essential modes of therapy*

*Counselling*

Before initiating treatment, the physician should prepare the patient by clearly communicating the medical reason (or reasons) for weight loss, tailored to the patient's specific problems. This approach enables patients to accept the concept of a healthy lifestyle, while de-emphasizing weight loss as the primary goal. It also helps the patient understand the physician's role in the program and realize that even modest weight loss can be beneficial. The physician should also explain the importance and benefits of realistic weight loss, as well as emphasize the importance of good, basic nutritional principles.

*Restriction of calories*

Caloric restriction can be moderate to severe, depending on the patient's health risk. A moderate caloric deficit or low-calorie diet (LCD; 800 or more calories daily) is indicated for most patients, while more severe caloric restriction (VLCD; 250 to 799 calories daily) is limited to those patients who are facing a major health risk.

A moderate caloric deficit or LCD is a first-line approach for obese patients who are attempting to lose weight for the first time. This regimen is also indicated for patients with a body mass index (BMI) of from 25 to 35, who have a good history of dieting (*i.e.*, may have failed at one attempt, but are motivated to lose weight).

Although an LCD is traditionally defined as a diet that provides caloric intake of approximately 1200 kcal/day for females and 1500 kcal/day for males, an individualized approach is more likely to succeed in clinical practice. For instance, an obese woman with an energy expenditure of 1500 kcal/day would lose one pound a week on a 1000 kcal/day diet, whereas an obese woman with a daily energy expenditure of 2500 kcal/day would lose approximately three pounds a week on the same diet.[2] Therefore, the physician and the dietitian should determine caloric requirements for each patient, based on daily energy intake, daily energy expenditure, and an average weight-loss goal of approximately one pound per week after the first month.[3]

The diet must be realistic, *i.e.*, based on dietary modification and practical changes in eating habits. The patients should also drink at least 1.5-2.0 liters of water daily,[3] unless cardiac disease (such as congestive heart failure), edema, or renal insufficiency is present. For patients with renal disease, diabetes, or other metabolic disorders, the physician should determine protein requirements. Energy restriction and weight loss may also necessitate changes in scheduling or dosage of medications such as orally administered glucose-lowering agents or insulin.

The diet is most likely to succeed when it is the patient's first attempt at losing weight. LCDs are safe for patients with comorbid conditions such as diabetes mellitus, hyperlipidemia, or hypertension; in such cases, the physician

should be actively involved in patient management. Food logs or record books should be completed by the patient and, if necessary, adjusted to ensure that the rate of average weight loss does not exceed, or fall short of, the weekly goal.

Potential complications include the following:[4] ketosis (if the diet contains < 100 g of carbohydrates daily), excessive loss of lean body mass, arrhythmias, dehydration, and a tendency for recidivism. On average, LCDs result in a total weight loss of 13-17 pounds during a period of 20-24 weeks.[5] However, some patients need to lose more weight, and may need to lose it more rapidly; in such cases, a VLCD may be necessary.

A VLCD is a liquid formulation or food diet that provides < 800 kcal/day.[6] A daily caloric intake of < 800 kcal/day is not usually recommended, because little evidence exists to show that VLCDs providing less energy will increase weight loss.[5] Just as with standard LCDs, the exact number of calories in the VLCD should be individualized.[7]

A VLCD is only appropriate when the patient faces a major health risk and the physician has determined that such a diet can be used safely. VLCDs are indicated for patients who meet specific criteria. They should have a high or very high health risk due to BMI alone (BMI ≥ 35) or BMI ≥ 30 in association with serious comorbid conditions (*e.g.*, congestive heart failure). The physician should not prescribe VLCDs to patients who have a BMI of 30, because such patients have an increased risk of negative nitrogen balance and a loss of lean body mass.[2,7]

Clearly, VLCDs are still associated with more side-effects and a greater risk of potentially serious complications than LCDs. Usually, however, they are only associated with minor complications when administered to carefully selected patients by experienced physicians.[8] When a VLCD is being prescribed, patients receiving drugs to treat diabetes or hypertension require close surveillance because doses of both types of medication will probably have to be reduced or discontinued. Cholelithiasis is the most frequent complication of VLCD therapy, occurring in up to 25% of patients on VLCDs,[9] and is most common when weight loss consistently exceeds three to five pounds per week. Serious complications can include excessive loss of lean body mass and sudden death in medically vulnerable persons who have comorbidities, especially if their daily caloric intake is < 600 kcal.

Patients who are prescribed a VLCD require close medical supervision.[11] The physician should see such patients at weekly consultations during the rapid weight-loss period and every two to four weeks thereafter. At each visit, the patients should undergo a basic serum chemistry evaluation, including electrolytes and liver function tests. This fairly intensive medical monitoring will help the physician detect that small minority of patients who may react adversely to the VLCD.[8] The physician often has to discontinue the administration of diuretics because of the increased risk of dehydration and electrolyte imbalance.[12]

VLCDs should not be used for longer than 12-16 weeks.[7] Longer-term VLCD programs can lead to excessive nitrogen loss (as the patient continues to lose weight), gallstone accretion, and relapse or recidivism. VLCDs can yield two to three times more weight loss than LCDs,[2] and the rate of this weight loss is usually greater. VLCDs usually produce weight loss of 3.3 pounds per week in females and 4.4 pounds per week in males, with the total loss after 12-16 weeks averaging 44 pounds. Improvements in glycemic control, decreases in systolic and diastolic blood pressure, and decreases in serum concentrations of total cholesterol, LDL-C, and triglycerides often occur within three weeks.[13] Although few long-term studies are available, long-term success with VLCDs does not seem to be any better than that with LCDs.[14,15]

*Lifestyle changes*

Counselling on lifestyle changes should be provided. This enables patients to evaluate and modify eating practices, physical activity habits, and emotional responses to weight.[2] Sessions should be conducted weekly,[2] or at least monthly, and should include a structured program with long-term follow-up. The LEARN manual is one of several useful guides for helping patients with behavior changes.

*Physical activity*

Although regular, moderate physical activity alone results in a limited weight loss of four to seven pounds in the long term,[4] it is an essential and high-priority element of any weight-management program. Regular physical activity is the most important predictor of long-term weight maintenance.[2,13,16] Correlational studies and randomized trials have shown that patients who diet and exercise regularly are much more likely to maintain weight loss than those treated by diet alone.[2,16]

When performed in combination with the restriction of calories, regular, moderate physical activity achieves the following results: increased energy expenditure; maintained or minimized loss of lean body mass;[3,4] reduced cardiovascular risk by producing beneficial changes in the lipid profile;[17] positive psychological effects, including stress reduction and an improved sense of well-being and optimism;[18,19] reduced insulin resistance;[20] and possibly other health benefits, even when the patient remains overweight.

The goal of any weight-management program should be at least 30 minutes of moderate-intensity physical activity five to seven times per week. Initially, several ten-minute periods of physical activity throughout the day (*e.g.*, a 30-minute daily aggregate of brisk walking,[21] aerobic physical activity such as exercise tapes, or housework such as vacuuming) performed three days per week may be more important than 30 minutes of continuous physical activity performed six days per week.

Patients who need to exercise but cannot do so because of a medical condition (*e.g.*, heart disease, pulmonary disease, severe degenerative joint disease,

morbid obesity, or traumatic injury) should be referred to a physician, therapist, or exercise physiologist for a tailored program of physical activity.

## Pharmacotherapy

The American Association of Clinical Endocrinologists (AACE) does not condone anti-obesity agent therapy when used simply for cosmetic purposes, or when weight loss can be achieved and maintained without pharmacotherapy. When needed to reduce a health risk, used in the context of long-term disease management, and prescribed and supervised by an experienced physician such as an endocrinologist, internist, or family practitioner, pharmacotherapy may increase the effectiveness of a basic weight-management program, and should be used only in conjunction with such a program. Although anti-obesity agents can improve weight loss, they may also be associated with adverse effects, even including the possibility of a fatal outcome.

Generally, the AACE only recommends prescribing Food and Drug Administration (FDA)-approved agents. The AACE does not advocate the use of any anti-obesity agent, prescription or otherwise, that has not undergone thorough clinical testing. Any administration beyond a few weeks (usually considered as three months), except for sibutramine, which may be given for up to one year, is an 'off-label' use. The physician should be aware of the recommended treatment duration, although long-term use of an appropriate anti-obesity agent may be necessary for successful, long-term maintenance of weight loss.

### *Weight loss*

Patients who take active drugs are more likely than those who do not to achieve a clinically significant weight loss of ≥10% of initial body weight.[22] However, approximately one-third of patients do not respond to pharmacotherapy.[23-25] Among responders, weight loss can vary widely, and it tends to plateau after approximately six to eight months.[23]

On average, anti-obesity agents produce a weight loss of four pounds in four weeks in responders.[23,26] When pharmacotherapy is initiated, a three-to-six-week run-in period can often predict a patient's responsiveness, inasmuch as weight loss during this period is a major indicator of success.[23] If patients do not lose weight during the run-in-period, the physician may discontinue pharmacotherapy because titration, even at maximal levels, apparently does not increase effectiveness.[23] This approach will minimize unnecessary exposure and risks.

### *Maintenance of weight loss*

Although their utility for weight loss has long been recognized, anti-obesity

agents have only recently been noticed as being useful for the long-term maintenance of weight loss.

Studies that have investigated the long-term (one to 3.5 years) effectiveness of anti-obesity agents (fenfluramine plus phentermine resin) have shown that these drugs helped to maintain reduced body weight in a substantial number of patients.[23,26] When pharmacotherapy was discontinued, the patients regained weight, and when medication was reintroduced, the patients achieved additional weight loss.[23,26]

*Recommended use of available agents*

Pharmacotherapy, in conjunction with a basic weight-management program, is suitable for patients with a BMI ≥30, or for patients with a BMI of 27 to 29 and at least one major comorbidity. Pharmacotherapy is contraindicated in pregnant or lactating women, patients with unstable cardiac conditions, those with uncontrolled hypertension, serious medical conditions, or psychiatric disorders, and patients taking other incompatible drugs.

*Anti-obesity agents approved for use for up to one year*

*Sibutramine*

A centrally acting anti-obesity agent, sibutramine blocks the re-uptake of norepinephrine, serotonin, and dopamine in nerve terminals in order to produce substantial weight loss and maintenance of loss of weight. It does not stimulate serotonin, norepinephrine, or dopamine release,[22] nor does it have an affinity for these receptors.[27,28] Sibutramine acts primarily through active amine metabolites to reduce food intake, and may increase energy expenditure.

The clinical efficacy of sibutramine has been evaluated in approximately 4600 patients worldwide. When administered in conjunction with a reduced-calorie diet, it is effective for weight loss and maintenance of weight loss for up to one year.[29,30]

Sibutramine is generally well tolerated, has a low abuse potential, and has not been associated with cardiac valvulopathy, primary pulmonary hypertension (PPH), or neurotoxicity. Most adverse events, including dry mouth, anorexia, and constipation, were transient and mild to moderate in severity.

Sibutramine should not be used in patients with uncontrolled or poorly controlled hypertension. It increases sympathetic nervous system activity through its norepinephrine re-uptake inhibition. Thus, increases in blood pressure or pulse rate (or both) can be anticipated. In placebo-control trials of obese patients, sibutramine (5-20 mg daily) was associated with mean increases in systolic and diastolic blood pressure of from 1-3 mmHg relative to placebo, and increases in pulse rate of 4-5 beats/min relative to placebo. Larger increases were seen in some patients, particularly when sibutramine treatment was initiated at higher doses.

Routine vital sign monitoring is recommended. Sustained, potentially clinically significant increases in blood pressure are usually detectable within the first month of treatment.[31]

Sibutramine, a potent serotonin and norepinephrine re-uptake inhibitor, should not be used in patients receiving monoamine oxidase inhibitors (*e.g.*, selegiline, tranylcypromine, and phenelzine) or centrally acting appetite suppressants (such as phentermine). Sibutramine should not be used in patients with a history of narrow-angle glaucoma or seizures. Additionally, patients with poorly controlled or uncontrolled hypertension, severe renal impairment, severe hepatic dysfunction, congestive heart failure, coronary artery disease, arrhythmia, or stroke, should not be treated with sibutramine, nor should it be given to patients who are being treated with medications that regulate the brain neurotransmitter, serotonin (such as fluoxetine, sertraline, venlafaxine, fluvoxamine, and paroxetine). 'Serotonin syndrome', a rare but serious condition, may develop in patients receiving other serotonergic agents (including sumatriptan succinate, dihydroergotamine, dextrometorphan, meperidine, pentazocine, fentanyl, lithium, and tryptophan).[32] To date, no cases of overdose or serotonin syndrome have been reported with the use of sibutramine.

*Anti-obesity agents approved for short-term use*

*Diethylpropion*

An anorexiant agent considered one of the safest for patients with mild to moderate hypertension, diethylpropion is effective in producing weight loss and is indicated for use for up to a few weeks.[33] In a clinical trial for 24 weeks involving 200 patients, diethylpropion-related weight loss ranged from 14.4-25 pounds (6.6-11.3 kg). Side-effects of the drug include mild restlessness, dryness of the mouth, and constipation. Less frequently, nervousness, excitability, euphoria, or insomnia may occur. Cases of psychological dependence have reportedly occurred with use of diethylpropion.[34]

*Mazindol*

Structurally related to the tricyclic antidepressant agents, mazindol seems to act by blocking norepinephrine re-uptake and synaptically released dopamine. It is effective as an appetite suppressant.[35] Loss of weight of 26.5-31 pounds (12-14 kg) versus 22 pounds (10 kg) for the placebo group of patients was reported in a one-year study.[36,37] The effects of long-term use of mazindol were a 15-pound (6.8 kg) mean weight loss, and improvement in systolic blood pressure, liver function (serum glutamic-oxaloacetic transaminase), triglyceride and cholesterol levels, and glucose tolerance. In the same study, 53% of obese subjects maintained weight loss with the use of mazindol after loss of weight from following a VLCD, but only 20% maintained that loss of weight without the use of mazindol. It can potentiate catecholamines, and caution is

required when it is being used in conjunction with sympathomimetic amines. Adverse reactions include stimulant effects similar to amphetamines; however, mazindol does not seem to cause euphoria, and the abuse potential is low. Insomnia, agitation, and dizziness are common during the use of mazindol. A small increase in heart rate (ten beats/min) is noted with orthostatic position change. Use in patients with severe hypertension or CVD is inappropriate.[38]

*Phentermine*

Phentermine has been evaluated in placebo-controlled and comparative studies, in which it was equal in efficacy to fenfluramina. The FDA has approved phentermine for short-term use (*i.e.*, a few weeks). Weight loss does not seem to be related to plasma drug concentrations. Titration of the dosage beyond 30 mg/day is unnecessary.[39] Phentermine monotherapy has been evaluated in studies for up to 36 weeks. No case reports have been published of heart valve abnormalities with use of phentermine alone. Few reports of PPH have been associated with phentermine used alone.[40]

*Over-the-counter anti-obesity products*

*Phenylpropanolamine*

The FDA considers phenylpropanolamine, an over-the-counter drug, to be safe and effective as an aid to weight reduction. This agent acts on the $\alpha_1$-receptor and is classified as a direct $\alpha$-adrenergic agonist with indirect catecholamine-releasing effects. Probably related to reduced lipid solubility, compared to amphetamines, it has little central nervous system stimulant effects, and its use has not been shown to result in the development of dependence. It is used systemically as an appetite suppressant. In a comprehensive obesity-management program, phenylpropanolamine increased weight loss by 0.25-0.5 pounds weekly compared to placebo in a one-week, controlled clinical trial.[41] The anorexigenic effectiveness of phenylpropanolamine may diminish after four weeks.[42]

The use of phenylpropanolamine is sometimes associated with adverse effects such as confusion, headache, nervousness, tachycardia, palpitations, and sleeplessness. It is not addictive at recommended doses. Used in excessive doses, it may produce altered perception or psychosis. Currently, its labelling warns that its use in patients with hypertension, depression, heart disease, diabetes, or thyroid disease should be under the supervision of a physician. Serious toxicity (*e.g.*, intracranial hemorrhage or severe hypertension) may occur in patients who take doses above the recommended. Use with monoamine oxidase inhibitors should be avoided.[43,44]

*Other products*

Apart from phenylpropanolamine, most over-the-counter products promoted for weight control are bulk-producing agents such as methylcellulose, carboxylmethylcellulose, psyllium hydrophilic colloid, polycarbophil, and natural fibers

(*e.g.*, wheat and oat bran). They produce a transient sense of fullness and can temporarily lessen the desire to eat (for about 30 minutes). These products are not absorbed into the system, but require large quantities of water and can increase peristalsis. Accumulation of mucilaginous bulk laxatives may also result in esophageal, gastric, small intestinal, or rectal obstruction, and they are not indicated in persons with pre-existing intestinal problems, those with difficulty swallowing, or patients on a carbohydrate-restricted diet.

Ephedrine is a sympathomimetic agent that, in short-term studies of small numbers of patients, has been shown to increase thermogenesis and promote weight loss, especially when combined with caffeine. It is marketed as a nutrition supplement, 'fat burner', or energy booster. The current popular use involves combining it with St. John's wort (a plant-derived serotonergic agent), and is being called the 'herbal fen-phen' and promoted as a weight-loss product (*e.g.*, ma huang).

Ma huang may have powerful stimulant effects on the heart and nervous system. The weight-loss claim has not been substantiated. Since 1994, the FDA has evaluated more than 900 reports of adverse effects (including several dozen of deaths) associated with use of 'ephedrine-alkaloid-containing products'. Some products contain the herb *Hypericum perforatum* (known as St. John's wort) or the compound 5-hydroxytryptophan, which is closely related to L-tryptophan. The actions and possible side-effects of St. John's wort have not been carefully studied. Finally, after they were linked to more than 1500 cases of eosinophilia-myalgia syndrome, these drugs were abandoned.

*Orlistat*

Orlistat is a lipase inhibitor called Xenical. This drug binds to the pancreatic lipase in the gut and makes it ineffective. Thus, partial fat malabsorption is induced.[45] The effects on the absorption of fat-soluble vitamins, particularly vitamins D and E, make vitamin supplementation advisable in some patients.[45] The drug may also cause oily stools as a result of increased fat in the lower gastrointestinal tract. Clinical trials of efficacy demonstrated clinically significant weight loss (5% more than with placebo) in slightly more than half the patients who received orlistat for up to one year.[46]

*Acarbose*

An orally administered agent that acts as an amylase inhibitor, acarbose delays or inhibits digestion of diglycerides and complex carbohydrates.

*Olestra*

A product of sucrose esterification with certain fatty acids, scheduled to be marketed during 1998, olestra is a non-digestible fat substitute that reduces

cholesterol absorption. Clinical data supporting its role in weight loss are inconclusive, although it has been shown to reduce LDL-C.[47] In one study, patients who received 30 g of their daily fat intake from this sucrose polyester lost a mean of 2.6 pounds during a period of 30 days.

## Surgical treatment of obesity

Two proven surgical options are available for the treatment of morbid obesity: *(1)* restrictive operations such as vertical banded gastroplasty (gastric stapling) or laparoscopic gastric banding; and *(2)* gastric bypass operations such as Roux-en-Y gastric bypass or extensive gastric bypass (biliopancreatic diversion).[48,49]

Other surgical options include intestinal bypass (effective but associated with major complications), jaw wiring (effective while used), and liposuction (cosmetic procedure). Gastric bubble and vagotomy have not been proved to be effective.[25,50]

The surgical treatment of obesity should only be considered in carefully selected patients who meet the following criteria: *(1)* existence of a very high medical risk (BMI > 40, or of 35 to 39 with life-threatening or disabling comorbid conditions such as diabetes mellitus, dyslipidemia, hypertension, or serious cardiopulmonary disorders);[51] *(2)* presence of obesity for at least five years; *(3)* no known history of alcoholism or of a major psychiatric disorder;[50] and *(4)* the patient is aged between 18 and 65 years.[50,52]

In such patients, a gastric surgical procedure can induce rapid and substantial weight reduction within one year postoperatively.[50] The accepted weight-loss goal should not be greater than 15% of the desired body weight.[50]

Vertical banded gastroplasty results in weight loss for at least two years,[50] but some of the weight lost may be regained within five years. The weight loss associated with vertical banded gastroplasty can also considerably reduce the comorbid conditions, including diabetes mellitus type 2, hypertension, respiratory distress, hyperlipidemia, and disability.[50,51]

Roux-en-Y gastric bypass produces more substantial weight loss than vertical banded gastroplasty. This procedure is a more complicated gastric bypass which successfully promotes weight loss, but is associated with a risk of nutritional deficiency.[53]

## Maintenance of weight loss

Maintaining weight loss seems to be more difficult than losing weight, particularly in patients who were treated with caloric restriction. It requires a lifelong commitment to a change in lifestyle, behavioral responses, and dietary practices.

Continued program contact, physical activity, nutritional sophistication, and

self-monitoring are four characteristics that were observed in men and women who successfully maintained a weight loss of 20% or more for two years.[54]

The medical reasons for weight loss and its maintenance should be strongly emphasized. A patient who experiences a reduction in comorbidities and an improved sense of well-being is more likely to be motivated to maintain weight loss. In addition, psychological therapy should be encouraged for patients experiencing negative life events or family dysfunction, both of which are negative predictors of the maintenance of weight loss.

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# OBESITY IN OBSTRUCTIVE SLEEP APNEA SYNDROME
## Dietary therapy and pharmacotherapy

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### Introduction

Obesity is a chronic condition of epidemic proportion, associated with increased morbidity and mortality.[1] Epidemiological studies have shown an increased relative risk of osteoarticular, gynecological, metabolic, cardiovascular and respiratory complications in obese individuals.[2,3]

In the majority of morbidly obese patients (body mass index (BMI) >40 kg/m$^2$), subclinical abnormalities of the respiratory function are present.[4] In some cases such abnormalities may become clinically relevant during sleep, as in the obstructive sleep apnea syndrome (OSAS), or be constantly present, as in the obesity-hypoventilation syndrome (OHS), with varying degrees of hypoxia, hypercapnia, pulmonary and systemic hypertension, coronary artery disease, arrhythmias and thromboembolic complications.

Despite the strong correlation between BMI and AHI (apnea + hypopnea index: a measure of OSAS severity), a threshold effect for BMI cannot be established. Weight excess and reduced respiratory compliance account for only 60-70% of variance.[5] Indeed, many factors contribute to the development of breathing abnormalities: sex, age, weight excess, obesity duration, fat distribution, anatomical variants of the upper airways, inadequate neuromuscular control, abnormal respiratory centers, chemoreceptors threshold, and endocrine milieu. It is not possible to demonstrate a linear correlation between $CO_2$ retention and the degree of adiposity, while there is a good correlation between $pCO_2$ and respiratory compliance; the hypocapnic individual has a compliance of about 70% lower than normal, while the normocapnic individual has a normal respiratory compliance regardless of the degree of adiposity.[5]

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For these reasons, the degree of weight loss able to induce a clinical improvement of the respiratory function is highly variable.[6] A 10% loss of initial weight, always advisable for its positive effects on cardiovascular and metabolic parameters, reduces the severity of OSAS by 50%; it is therefore clear that weight reduction is of paramount importance in the management of OSAS.[7]

A universally accepted obesity classification (degree and fat distribution) and general principles for appropriate dietary interventions will allow a common background for future research on OSAS and OHS treatment.

## Evaluation of weight excess and fat distribution

OSAS prevalence is higher in the obese population. On the other hand, 50% of OSAS patients are of normal weight.[8] Therefore, in order to better understand the pathogenic role of obesity in OSAS, it is important to evaluate not only the degree of fat excess, but also its distribution (visceral or subcutaneous) and its localization near the upper airways, particularly in the anterolateral position.[8]

Fat excess is estimated by the BMI, *i.e.*, the ratio between weight in kilograms and height in square meters ($kg/m^2$). Of all the indices, BMI has the highest correlation to weight and fat mass and is the least correlated to height.[2,9] The strong correlation between BMI and cardiovascular mortality makes it particularly useful for clinical purposes.[1]

The relative risk increases when, at the same BMI value, fat has a more visceral distribution. Measurement of waist circumference (at the midpoint between the lower border of the rib cage and the iliac crest) is correlated with visceral fat mass, while hip circumference (the largest in the gluteal region) is correlated with subcutaneous fat mass.[10] When the absolute value of waist circumference (WC) is ≥102 cm in males and ≥88 cm in females (WHO), or when the waist-hip ratio (WHR) is ≥1.0 in males and ≥0.85 in females, obesity is defined 'visceral'.[1,7,10]

In addition, in snorers neck circumference is considered to be strongly predictive of OSAS when it is >43 cm in males and >40 cm in females.[7]

Table 1 shows the relative risk of diabetes type 2, hypertension and coronary heart disease (CHD) in relation to BMI and WC;[1] the risk of hypertension and CHD is further increased when OSAS is present. Therefore, it is necessary to include the appropriate questions during the first encounter with obese patients in order to detect OSAS.

Table 2 shows our data in a group of 148 patients with a BMI >40 $kg/m^2$ seen at an obesity clinic for a preoperative evaluation for possible bariatric surgery (gastric banding); on checking histories, OSAS was found in 11.5% of the patients (12 males and five females, average age 41 ± 11 years) with a BMI of 51.9 ± 16 $kg/m^2$ in males and 47.7 ± 8 $kg/m^2$ in females; WC was 154 ± 38 cm in males and 128 ± 16 cm in females, and WHR 1.03 ± 0.16 in males and 0.90 ± 0.14 in females; nine subjects had hypertension (blood pressure above 140/80 or who were on antihypertensive treatment); in two subjects the blood pressure could not be recorded due to the extremely large arm circumference.

*Table 1.* Overweight and obesity classes and relative risk correlated with BMI, WC* and the presence of OSAS**

| *Definition* | *BMI kg/m²* | *Obesity class* | *Relative risk* | | |
|---|---|---|---|---|---|
| | | | *WC** | *OSAS*** | |
| | | | *males ≥102 cm females ≥88 cm* | *males >102 cm females >88 cm* | |
| Underweight | <18.5 | | | | |
| Normal weight | 18.5–24.9 | | | increased | increased |
| Overweight | 25–29.9 | | increased | high | high |
| Obesity | 30–34.9 | I | high | very high | very high |
| | 35–39.9 | II | very high | very high | very high |
| | ≥40 | III | extremely high | extremely high | extremely high |

*risk of diabetes type 2, hypertension and CHD; **risk of hypertension and CHD
(Modified from WHO. Obesity. Prevention and management of the global epidemic. Report of a WHO consultation on obesity. Geneva 3rd-5th June, 1997, WHO, Geneva)

*Table 2.* Clinical characteristics of morbidly obese patients with or without a history of OSAS

| *Group* | *n* | *BMI* | *WHR* | *WC (cm)* | *Hypertension prevalence (%)* |
|---|---|---|---|---|---|
| All males | 40 | 47.8 ± 16 | 1.03 ± 0.16 | 145 ± 32 | 28 |
| All females | 108 | 43.5 ± 14 | 0.90 ± 0.14 | 121 ± 30 | 22 |
| Males with OSAS | 12 | 51.9 ± 16 | 1.04 ± 0.16 | 154 ± 38 | >50 |
| Females with OSAS | 5 | 47.7 ± 8 | 0.94 ± 0.10 | 128 ± 16 | 40 |

## Dietary therapy

Planning an adequate dietary regimen implies an estimate of daily energy expenditure in order to achieve an adequate caloric deficit and obtain a gradual weight loss.

When measuring resting energy expenditure (REE) by indirect calorimetry, Ryan *et al.* did not show clinically significant differences between obese subjects with and without OSAS, when REE was corrected by lean body mass (LBM) units.[11] It is not possible to demonstrate any difference between normal weight individuals and stable weight obese patients with OSAS.[12] Stenlof *et al.* measured 24-hour energy expenditure (24hEE) in calorimetric chambers and, in OSAS patients, found an increased energy expenditure during sleep; this increase was normalized by nasal continuous positive airway pressure (CPAP).[13] In all cases, the mechanical work of breathing may be increased two- to three-fold, even in eucapnic subjects.[5]

Since the only means of reducing body mass is to induce a negative energy balance, it is necessary to calculate the basal metabolic rate (BMR) and the physi-

cal activity level (PAL) in each subject. BMR can be estimated by predictive equations which take into account sex, age, weight, height, while, for 24hEE, average PAL values referred to lifestyles such as light, moderate or heavy physical activity, expressed as multiples of BMR, can be used.[14,15]

Balanced caloric deficit diets are defined when they have ≥1200 kcal/day; low calories diets (LCD) between 1199 and 800 kcal/day and very low calories diets (VLCD) below 800 kcal/day.[16]

Since dietary therapy results must be evaluated after an adequate interval (≥1 year), we can state that there are no significant differences between balanced caloric deficit diet and VLCD.[7] This means that the initial advantage of VLCD is completely lost after one year, due to the more rapid weight regain, with subsequent wider weight fluctuation (weight cycling syndrome).[17]

We must therefore avoid an energy deficit higher than 500-1000 kcal/day (for 24hEE) or a total energy intake lower than the BMR.[7] In this way, we will minimize lean mass loss, avoid excessive dehydration, and prevent the psychobehavioral disturbances underlying the weight cycling syndrome. With the knowledge that 1 kg of adipose tissue corresponds to about 7200 kcal, a monthly weight loss of about 3-5 kg is the optimal rate.[17]

VLCD may be justified for initially improving the symptoms in OSAS patients, but must be carried out under medical supervision (electrolyte disturbances, orrthostatic hypotension, ketoacidosis, and essential nutrient deficits) and followed by balanced caloric deficit diets associated with increased physical activity appropriate for the cardiorespiratory condition of the patient and with cognitive-behavioral modifications.

Caloric intake must be supplied by a balance of energetic nutrients: carbohydrates and proteins (4 kcal/g) and fats (9 kcal/g). Protein calories must be distinguished from carbohydrate and lipid calories, because they are chiefly utilized not for energy purposes but for maintenance (turnover) and growth of lean mass. In adults, the recommended dietary allowances (RDA) for proteins is 0.8-1 g/kg desirable body weight (about 70 g/die for males and 50 g/die for females), enough to cover the needs of healthy individuals even when practising sports activities.[14] Subjects must be given 50% animal and 50% vegetable proteins, thus avoiding an excess of animal fat and achieving a good balance of essential and non-essential amino acids.[17]

Once the protein requirement is met, the remaining calories may be supplied by carbohydrates (70%) and fats (30%). Carbohydrates are subdivided in complex carbohydrates (80%) and simple sugars (20%), *i.e.*, saccharose (sugar), fructose (present in fruits) and lactose (present in milk).

When prescribing a hypocaloric diet, it is also necessary to evaluate the absolute amount of carbohydrates since, in a healthy adult, under physiological conditions 140 g of glucose is consumed daily by the brain and 40 g by the erythrocytes.[14] A diet low in carbohydrates, and therefore hyperlipidic, induces a metabolic shift with accumulation of ketone bodies, metabolic acidosis and hyperventilation.[17] Carbohydrate oxidation, although producing more $CO_2$ for the same $O_2$ consump-

tion when compared to fat oxidation, is more easily tolerated by patients with OSAS; for these reasons, carbohydrates can be defined 'necessary', even if 'non-essential' nutrients (they may be produced by gluconeogenesis). They should be given in a total amount of at least 100 g/day for their protein-sparing effect.

Fat intake must be limited to 30% of the total caloric intake.[14] Intake of saturated fats (≤10% of total calories) and essential fats (linoleic acid: n-6, and α-linolenic acid: n-3) should be determined according to the Italian RDA for a normocaloric diet.[14] The total fat intake should be reduced and divided in: saturated fats 34%, mono-unsaturated fats 50%, and poly-unsaturated fats 16%; from the nutritional point of view, this meets the requirements for essential fatty acids (EFA) and liposoluble vitamins (α-tocopherol, β-carotene, vitamin D), of which the alimentary fats represent the transport mechanism for absorption. From a practical point of view, it is usually sufficient to recommend splitting fat intake into 50% animal and 50% vegetable origin, in order to follow the proportions mentioned above, since animal fat is about two-thirds saturated and one-third mono-unsaturated, while vegetable fat is one-third saturated and two-thirds mono- and poly-unsaturated.[17]

## Conclusions

The medical treatment for obesity complicated by OSAS is based on nutritional modifications that include a balanced caloric deficit achieved by dietary intervention, cognitive behavioral modifications, and a level of physical activity appropriate to the weight excess and respiratory dysfunction, in order to ensure prevention of weight regain in the long term. Anorectic drugs are not recommended due to their possible effects on the cardiovascular system, while inhibitors of fat absorption, such as orlistat ((N-formil-L-leucine(s)-1-(((2S,3S)-3-esil-4-ossi-2ossietanil) metil)dodecil ester), could be added to the regimen.

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# HIGHLIGHTS IN OBESITY

# ENDOCRINE ABNORMALITIES IN OBESITY

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## Introduction

Obesity could well become the most common health problem of the 21st century. The prevalence of obesity is increasing in westernized societies and, in the USA, the age-adjusted prevalence of BMI > 30 kg/m² increased between 1960 and 1994 from 13 to 23% in people over 20 years of age, and has been attributed to an increased fat intake and/or decreased physical activity. However, the role of dietary factors on human obesity has been challenged. High-fat diets, due to their high energy density, stimulate voluntary energy intake which in turn does not stimulate its own oxidation, but rather fat storage in the human body. When diet composition is isoenergetically switched from low to high fat, oxidation increases only slowly, resulting in positive fat balances in the short-term. Together with a diminished fat oxidation capacity in pre-obese subjects, high-fat diets can therefore be considered to be fattening. Another environmental factor which could explain the increasing prevalence of obesity is the decrease in physical activity. The percentage of body fat is negatively correlated with physical activity, and exercise has pronounced effects on energy expenditure and substrate oxidation. High-intensity exercise, due to a decrease in glycogen stores, can lead to a rapid increase of fat oxidation, which could compensate for the consumption of high-fat diets in westernized societies.

Although the consumption of high-fat diets and low physical activity may determine obesity, there is still considerable inter-individual variability in body composition in individuals on similar diets, which can be attributed to the genetic background.[1] In fact, obesity can occur as a result of genetic or acquired changes in three main types of biochemical processes: *(a)* feeding control, which determines the sensation of satiety and hunger through processes that depend on an interplay between internal signals (notably leptin) and environmental factors; *(b)* energy efficiency, in particular the activation of thermogenesis mediated by uncoupling proteins (UCPs) that dissipate part of the energy con-

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tained in food in terms of heat instead fat; and *(c)* adipogenesis, the process by which cells specialized in fat storage (adipocytes) are formed, which is controlled by an interplay of transcriptional factors, including members of the C/EBP, PPAR-λ and ADD families.[2]

## Central control of energy homeostasis

Adipocytes – the primary site for energy storage and release – were long suspected to play an active role in regulating body weight homeostasis and energy balance. As a result, many studies have focused on possible abnormalities in adipocyte physiology and metabolism. An ever-increasing body of evidence indicates that, in addition to serving as a repository for energy reserves, adipocytes secrete a myriad of factors that comprise a complex network of endocrine, autocrine, and paracrine signals.[3] Through this network of signals (hormones, growth factors, cytokines and protein that are related to the immune system and vascular functions), they participate in the regulation of energy homeostasis, host defence, and reproduction, and may also contribute to the development of pathological states, such as insulin resistance.

Food intake is controlled by separate but interacting groups of molecular signals. One group, the so-called satiety signals, is proportional to what is being consumed, and regulates food intake. Cholecystokinin is the best known of this group, and its administration before a meal causes a dose-dependent reduction of food intake. In itself, however, cholecystokinin (and other satiety signals) has little impact on body-fat stores. In the second group, the adiposity signals circulate in proportion to body adiposity and enter the brain, where they interact with satiety signals in the brainstem and hypothalamus. Insulin and leptin are the best known of these adiposity signals, and their intracerebroventricular administration in animals causes a dose-dependent reduction of both food intake and body weight. Within the brain, parallel but opposing pathways originating in the hypothalamic arcuate nuclei integrate adiposity signals with satiety signals. Those with a net anabolic effect increase food intake and reduce energy expenditure, and are basically represented by neuropeptide-Y; those with a net catabolic effect decrease food intake and energy expenditure, and are basically represented by melanocortin.[4]

## Peripheral control of energy homeostasis: adipose tissue as an endocrine organ

Recent clinical and experimental data have radically modified the concept of adipose tissue solely being devoted to energy storage and release. Adipose tissue is a target organ for glucocorticoids. An innovative finding is that adipose tissue produces cortisol from its inactive precursor, cortisone. Cortisol is a

modulator of food intake and glucose utilization; it interacts with selected receptors located in the hypothalamic nuclei and determines transcription of the NPY gene which, in turn, determines an increasing intake of carbohydrates. The hypercortisolism state is characterized by an increase of visceral adipose tissue.

Identification of leptin, a hormone synthesized by adipose tissue, has ushered in the modern view that it is a true endocrine organ. Leptin is produced by subcutaneous and, to a lesser extent, by visceral adipose tissue. It has a central role in body weight and especially in the regulation of fat stores, but it is also involved in several complex functions, including the physiological processes associated with puberty and gonadal steroidogenesis.

Angiotensinogen (AGT) is another hormone which is synthesized in abundance by adipose tissue and is produced in larger amounts by visceral than by subcutaneous fat. In addition, in humans and animals, adipose tissue appears to possess the entire renin-angiotensin system (RAS), suggesting that angiotensin-II, the final effector of the system, is produced locally. The function of adipose RAS is not well known as yet; besides participating, together with other hormones and substances, in adipocyte differentiation and fat tissue growth, it could be involved in the pathogenesis of the complications of obesity.[5]

## Obesity and neuroendocrine abnormalities: central role of the hypothalamic-pituitary-adrenal axis

Visceral obesity is mostly associated with the risk of co-morbidities. This is due to neuroendocrine perturbations, where the hypothalamic-pituitary-adrenal (HPA) axis plays a central role. The hyperactivity of the HPA axis, referred to as 'functional hypercortisolism', appears to be the result of two distinct mechanisms. The first, which appears to be central in origin, is characterized by altered ACTH pulsatile secretory patterns and by the hyper-responsiveness of the HPA axis to different neuropeptides, acute or chronic stress events and, possibly, to selected dietary factors. The other appears to be located in the periphery, specifically in the liver and visceral adipose tissue, and is characterized by supranormal cortisol production, whose paracrine and endocrine effects are well known and by hyperactivation of the sympathetic nervous system. The effects of cortisol hypersecretion, in combination with the consequent reduction of growth and sex steroid hormone production, determine a cascade of neuroendocrine-endocrine perturbations which lead to insulin resistance as well as to visceral accumulation of body fat. The blood pressure will also be elevated, which may be a consequence of central stimulation of the sympathetic nervous system, with the added effects of insulin. This results in a hypothalamic arousal, with the metabolic syndrome as a consequence.[6]

## Obesity and growth hormone

Obese subjects show a marked decrease in plasma growth hormone (GH) levels. However, the mechanisms by which increased adiposity leads to an impairment of GH secretion are poorly understood. Recent evidence suggests that adipose tissue may significantly influence GH secretion via two different signals, namely free fatty acids (FFA) and leptin. FFA appear to inhibit GH secretion mainly by acting directly at a pituitary level. Interestingly, reduction in circulating FFA levels in obese subjects led to a marked increase in GH responses to different GH secretagogues. This indicates that FFA exert a tonic inhibitory effect which contributes to blunted GH secretion in obese subjects.

Recent data have shown that leptin is a metabolic signal that regulates GH secretion, since the administration of leptin antiserum in adult rats led to a marked decrease in spontaneous GH secretion. However, leptin prevents the inhibitory effect exerted by fasting on plasma GH levels. The effect of leptin in adult rats occurs at a hypothalamic level by regulating growth hormone releasing hormone (GHRH), somatostatin, and NPY-producing neurones.[7]

GH regulates the expression of GH receptor and the synthesis of insulin-like growth factor-1 (IGF-1) in adipocytes. Although GH hyposecretion in obesity may decrease the generation of IGF-1 in each adipocyte, increased amounts of IGF-1 and GH-binding protein could be secreted from the excessively increased amounts of adipose tissue. This may contribute to the normal/high serum IGF-1 and high GH-binding protein levels in obesity. Favorable effects of GH treatment have been observed in GH-deficient obese children and adults. GH treatment decreases adiposity, reduces triglyceride accumulation by inhibiting lipoprotein lipase, and enhances lipolysis both via increased hormone-sensitive lipase activity and via induction of β-adrenoreceptors. GH treatment also has a favorable effect on obesity-associated dyslipidemia, but the effects on insulin sensitivity have been conflicting.[8]

## Obesity and steroid hormones

In humans, steroid hormones have been closely related to the regulation of adiposity, either through direct or indirect physiological mechanisms. Evidence also suggests a direct relationship between sex hormones and risk factors for cardiovascular disease. Male obesity and excess abdominal adipose tissue accumulation is associated with reduction in gonadal androgen and low adrenal C19 steroid concentrations. Reduced C19 steroids are also related to an altered metabolic risk factor profile including glucose intolerance and an atherogenic dyslipidemic state. In females, menopause-induced oestrogen deficiency and increased androgenization are associated with increased visceral obesity and with concomitant alterations in the metabolic risk profile. The increased amount

of adipose tissue in the intra-abdominal region coincident with the onset of the menopause may explain part of the increased risk of cardiovascular disease in postmenopausal females. In both males and females, plasma levels of sex hormone-binding globulin (SHBG) are strongly correlated with obesity and risk factors for cardiovascular disease, and more importantly, the relationship between low SHBG and altered plasma lipid levels appears to be independent of the concomitant increased levels of visceral adipose tissue. SHBG concentration may, therefore, represent the most important and reliable marker of the sex hormone profile in the examination of the complex interrelation between sex steroid hormones, obesity, and risk of cardiovascular disease.[9]

## Obesity and prolactin

In human physiology, outside pregnancy, the alteration of prolactin secretion is associated with an increase in body weight in both children and adults. In these circumstances, prolactin appears to be marker of the hypothalamic-pituitary function: the prolactin response to insulin hypoglycemia, thyrotropin-releasing hormone stimulation, and other stimulatory factors may be diminished. In addition, obesity alters the 24-hour spontaneous release of prolactin with a generalized dampening of release. A number of explanations have been given as the possible cause of these alterations, but it seems likely that they reflect obesity *per se* and are also associated with a concomitant state of hyperinsulinemia. Weight reduction, with accompanying decrease in plasma insulin levels, leads to normalization of prolactin responses in most, but not all, cases. To date, no molecular basis linking prolactin with increasing body fatness, weight, and appetite has been identified: new data suggest a possible link between fasting plasma prolactin and leptin concentrations in obese males.[10]

## Obesity and thyroid hormone metabolism

In obese subjects, serum thyroid hormone concentrations and their metabolic rate are within the normal range. Also, serum TSH concentrations and their response to TRH are normal, suggesting that tissue availability for thyroid hormones is normally preserved in these subjects. In contrast, during caloric restriction, serum $T_3$ concentrations decrease as a consequence of their reduced production rate from peripheral deiodination from $T_4$. On the other hand, serum $rT_3$ concentrations markedly increase as a result of their decreased metabolic clearance rate. During caloric overfeeding, serum $T_3$ concentrations increase, while serum $rT_3$ concentrations decrease. In this condition, the production rate of $T_3$ increases. During caloric restriction and overfeeding, serum $T_4$ concentrations and their production and degradation are not modified.[11]

## Metabolic complications of obesity

The rising prevalence of obesity is accompanied by an increasing number of patients who incur the metabolic complications of obesity, referred to as the 'metabolic syndrome', characterized by the simultaneous presence of obesity, insulin-resistance, hypertension, dyslipidemia, and a prothrombotic state. It has been shown that obese patients characterized by a high accumulation of visceral adipose tissue have increased glycemic and insulinemic responses to an oral glucose load compared to normal-weight individuals or to obese individuals with a low accumulation of visceral adipose tissue. Viscerally obese patients are also characterized by an unfavorable plasma lipid profile, which includes elevated triglyceride and apolipoprotein B concentrations, reduced HDL-cholesterol levels, as well as an increased proportion of small, dense LDL particles.[12] The clinical consequences of the metabolic syndrome are higher coronary heart disease and risk of stroke, type 2 diabetes and its complications, fatty liver, cholesterol gallstones, and possibly some forms of cancer. The key-point of the metabolic syndrome is represented by insulin resistance, which in turn determines the generalized derangement of all metabolic pathways.[13]

## Obesity and hormone abnormalities in obstructive sleep apnea syndrome

It is well known that there is high incidence of obstructive sleep apnea syndrome (OSAS) among obese patients. OSAS in obesity represents a risk of sudden death, and obese males with a history of OSAS have a high risk of sudden cardiovascular death, despite the absence of conventional risk factors.[14] It is commonly felt that these alterations are obesity-related, and it is known that very low calorie diet-induced weight loss has favorable effects on glucose tolerance, insulin resistance, and hypertension, and that it is an effective treatment for OSAS.[15] It is interesting to observe that, in the ob/ob mouse, which is characterized by obesity and is unable to produce leptin, measurements of respiratory function show that obesity is associated with impaired respiratory mechanics and depressed respiratory control, particularly during sleep. Longitudinal studies and leptin replacement studies in the ob/ob mouse indicate that leptin may act both as a growth factor in the lung and/or a neurohumoral modulator of respiratory control mechanisms. A relative deficiency in leptin, or a state of leptin resistance, may play a role in obesity-related breathing disorders.[16]

Other studies have focused on OSAS and thyroid metabolism. There is a high incidence of sleep apnea among hypothyroid patients. Thyroxin treatment could help in making these apneas disappear in the majority of cases, even if a few hypothyroids develop sleep apnea despite achieving the euthyroid state.[17]

Melatonin has a strong circadian rhythm with high values during the nighttime and low values in the afternoon. Afternoon serum-melatonin levels have been studied in patients with sleep-disordered breathing and normal controls. Compared to normal controls, patients suffering from OSAS had significantly higher serum-melatonin levels in the afternoon. These results indicate that breathing disorders in general may affect pineal function.[18]

Finally, many studies were carried out on the effects of OSAS-induced chronic nocturnal hypoxemia, on the hypothalamic-pituitary-testicular axis, the hypothalamic-pituitary-thyroid axis, and on catecholamine and cortisol secretion, and it has been found that nasal continuous positive airway pressure (nCPAP) treatment of OSAS patients for seven months normalized the plasmatic alterations found in basal LH, testosterone, cortisol, TSH, PRL, and their stimulated levels after the TRH challenge test, as well as the plasmatic and urinary alterations found in catecholamine levels.[19]

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# EVALUATION OF OBESITY IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA SYNDROME

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## Introduction

Obesity is a complex multifactorial condition in which excess body fat may put a person's health at risk.

In particular, obstructive sleep apnea syndrome (OSAS) is a common disorder that occurs in obese patients, and potentially fatal systemic illnesses frequently associated with this disorder include hypertension, pulmonary hypertension, heart failure, nocturnal cardiac dysrhythmias, myocardial infarction, and ischemic stroke.

An obstruction is caused by excessive fat deposits in the palate, and by a thick neck, and may produce repetitive episodes of complete or partial upper airway obstruction, leading to no or diminished airflow into the lungs.

## Evaluation

*Endocrine and metabolic evaluation*

*Lipid profile*

- total cholesterol: (maximum value, 220) a colorimetric enzymatic assay. Requires fasting for 12 hours and no alcohol consumption for 24 hours.
- HDL-cholesterol: (normal value, 30-75 mg/dl) the same assay for cholesterol fraction, bound with high density lipoproteins. Requires fasting for 12 hours, no alcohol consumption for 24 hours, and no excessive physical activity.
- LDL-cholesterol: (normal value, 100-160 mg/dl) the fraction bound with low density lipoproteins. Same requirements as for the HDL assay.
- triglyceride:

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- blood-glucose: (normal value, 70-105 mg/dl) an enzymatic UV method. Requires fasting for eight hours at least.
- insulinemia: (normal value, 5-20 mcU/ml) a radioimmunological assay (RIA). Twelve hours are necessary for evaluation.
- TSH: (normal value, 0.2-4 mU/l) an ultrasensitive immunoradiometric assay (IRMA). Salicylic acid, corticosteroids, androgen hormones, heparin, phenytoin, sulfamides, and thyroid hormones decrease TSH levels. Lithium carbonate, potassium, methadone, heroin, antithyroid drugs, estrogens, hormones, and pregnancy increase TSH levels.
- FT3: (normal value, 2-4 pg/ml) a proportion of free triiodothyronine, not bound to TBG, TBPA, albumin; a RIA; levels decrease with androgens and glucocorticoid therapy, salicylic acid, phenytoin, sulfamides, PTU, and heparin; levels increase with pregnancy or estrogens and thyroid hormone therapy, and with heroine and methadone intake.
- FT4: (normal value, 7-19 pg/dl) a proportion of hormone not bound to proteins; a RIA. Levels decrease and increase as for FT3.

## Aims of the study of body composition

Measurements of body composition yield data regarding normal growth, maturity, and the process of aging. Practically, these measurements provide standards against which departures from normality can be judged. It is necessary to define differences between genetic groups, sexes within each group, systematic variations with age and body size, and distribution of the seemingly random differences between individuals which remain unexplained. A knowledge of the range of normality is of value when studying trends in disease processes and monitoring the response to treatment. Body composition data may influence the choice of the most appropriate treatment in wasting illnesses, sepsis, trauma, renal failure, and nutritional disorders.

*Indirect methods*

- anthropometry (BMI and WHR)
- skinfold anthropometry
- hydrodensitometry
- bioelectrical impedance analysis (BIA)
- total body electric conductivity (TOBEC)

*Direct methods*

- computerized tomography (CT)
- magnetic nuclear resonance (MNR)
- dual-energy X-ray absorptiometry (DEXA)

*BMI* (body mass index) is the correlation between weight and height ($kg/m^2$) N.V. in females aged from 19-24 years and in males from 20-25 years.

*WHR* (waist-to-hip ratio) is

*Skinfold anthropometry* is a method devised to estimate body fat in subjects who are ill or unwilling to undergo immersion in water. It assumes a fixed relationship between total body fat (TBF) and the thickness of subcutaneous fat at certain sites. The sites chosen are usually at the mid-upper arm over the biceps and triceps muscles, and subscapular and supra-iliac sites, at which the thickness of a skinfold is measured with callipers. The mean values of the skinfold thicknesses at two or more sites has been related to body density in normal subjects measured by underwater weighing, and an identical relationship is subsequently assumed to estimate body density in other subjects. This relationship usually takes the form: Density = A-B $\log_{10}$ S, where A and B are empirically derived coefficients and S is the sum of the skinfold measurements (Womersley[1]).

While this technique is applicable in the clinical situation and is reproducible, subject to errors in the operator's measurement technique (standard deviation, 0.3 kg for TBF in all individuals), it assumes a constant relationship between subcutaneous fat at the sites measured and TBF, and still makes assumptions about the density of the fat-free mass (FFM). The biological component of the residual error makes the technique inaccurate over the whole range of body sizes, but especially in the extremes of depletion and obesity, respectively overestimating fat in wasted individuals and underestimating body fat in very obese subjects. In patients suffering from a fluid overload, subcutaneous edema may be erroneously included in the skinfold measurement. It has been observed that the ratio of subcutaneous fat to TBF may vary from 20% to 70% in normal subjects, so that the fundamental assumption of this technique may be wrong.

*X-ray computed tomography*

Computerized X-ray tomography uses a fan-shaped beam of X-ray incident upon the subject, and a linear array of detectors positioned along an arc on the far side of the subject, in order to detect the radiation transmitted. The X-ray source is rotated around the subject, and either the detector array is moved simultaneously, or a 360° arc of detectors is employed. The transmitted intensity contains information about internal structures traversed within the selected slice through the subject, which can be reconstructed as an image by a process of backprojecting from each angle to which the source-detector system was aligned. However, such a reconstructed image contains severe artifacts due to the overlapping of consecutive projections. Many methods have been devised to remove these artifacts, but the conventional method is to modify each projection with a convolution function, containing negative components, so that the sum of all the convolved backprojections eliminates the artifacts from the final image.

Consecutive slices through the subject's body can be imaged in this way, and masses of tissues and organs deduced from the sum of the areas occupied in each slice and the known densities of these tissues.

Each pixel of each slice is assigned an attenuation value, in terms of Hounsfield units (HU), ranging from –1000 HU (air) to 2000 HU (dense bone) with lipid at –191 HU, water at 7.5 HU, and protein at 349 HU. Adipose tissue occupies a range –190 to –30 HU, muscle, skin, and viscera range from –29 to 151 HU, and spongy to dense bone from 512 to 2000 HU. Sjöstrom[2] showed that total body tissue and organ masses could be determined from CT slices performed at 10-cm intervals from the toes to the fingers, with the supine subject lying with arms above the head. The reproducibility from repeated measurements of the same subject was good, with an error of 0.6% between paired scans. The sum of the estimated mass of body components was within 1% of body mass.

Since the low-energy part of the incident X-ray spectrum is preferentially attenuated, corrections have to be made for bean 'hardening' when determining the masses of adipose and other soft tissues and organs from the areas they occupy in tomographic images. Failure to apply such a correction would cause underestimation of the areas occupied by soft-tissue components, particularly in slices containing significant areas of bone mineral.

This method can produce multicompartment models of the human body. Adipose tissue can be divided into subcutaneous and intestinal or visceral components, and regional masses of muscle and the various organs can be computed. Anthropometric factors can be calibrated from the results of multislice CT images, and used to assess cardiovascular risks and responses to various treatment regimes in longitudinal studies. However, the radiation dose per slice imaged, leads to a preference for MRI in the longer term, although CT scan time is lower, the cost of the facility lower, and the method superior for accurate determination of visceral adipose tissue. This may in part be due to the lower risk of movement artifacts in CT than in MRI, and the possibility of the slight distortion of MR images due to non-linearity of the magnetic field gradient.

*Magnetic resonance imaging*

When a human body is inserted into a strong magnetic field, the atomic nuclei containing unpaired nucleons tend to align themselves with or against the applied field. Although only a small minority of nuclei are so aligned, they represent sufficient numbers for their response to a changing magnetic field to be detected outside the body, by coils tuned to the frequency at which these nuclei precess or wobble. The frequency at which the nuclei of a particular element precess in the applied magnetic field, the Larmor frequency, is directly proportional to the local strength of that field. When a linear magnetic field gradient is applied across the human body in a particular direction, the nuclei precess at a frequency determined by the local field strength. In this manner, the intensity

of the signal received at any frequency over the range of frequencies, gives a measure of the number of nuclei at each position along the direction in which the field gradient is applied. Also, a slice of tissue perpendicular to the magnetic field gradient may be selected by exciting those nuclei at the appropriate Larmor frequency. The magnetic field gradient may be applied in any of the three orthogonal directions, so that slices of tissue perpendicular to the gradient are selected.

When the orientation of the nuclei is caused to flip by the temporary application of a field at the Larmor frequency perpendicular to the main field, and afterwards allowed to relax towards their original orientation, the number of processing nuclei at any location is given by the signal strength at the corresponding frequency. Fourier analysis is used to transform the relaxation with time into the frequency domain, giving the signal strength as a function of frequency. Since the density of hydrogen protons does not differ greatly between fat and lean tissues, there would be little contrast between these tissues in images based on only the number of nuclei processing at any given frequency. The time constant of the decay to the original orientation is determined by the loss of energy to the environment of each nucleus, which is determined by its chemical bonding and the size and motion of the molecule of which it forms a part. Thus, hydrogen nuclei in free water molecules have long relaxation times (around 3 sec), whereas those in protein and lipids lose energy to the environment more rapidly. If the signal from the relaxing nuclei is sampled during a shorter interval after excitation than is necessary for complete relaxation, there is a larger signal from those nuclei with a longer relaxation time. In this manner, contrast between hydrogen in water and in other tissue, and between tissue with different (proton) relaxation times can be achieved.

The process of relaxation or reorientation of nuclear spins after excitation comprises two components, the spin-lattice or longitudinal relaxation time ($T_1$) for the spin component parallel to the main magnetic field, and the spin-spin or transverse relaxation time ($T_2$), for the spin component perpendicular to the main field. The contrast in images based on differences of $T_1$ between tissues can be enhanced by first applying a doubly long excitation pulse that changes the orientation of nuclear spins by 180° (180° pulse), then after a short interval, applying a 90°-pulse, and after an equal interval, sampling the subsequent relaxation, a process known as inversion recovery.

A 90° excitation pulse (of a duration of a quarter of a period at the Larmor frequency) tends to orientate nuclear spins perpendicular to the main magnetic field. After the pulse, these relax towards a random lateral orientation, due to the interaction between adjacent nuclei, with a time constant $T_2$. If, after a short time interval, a doubly long excitation pulse is applied (a 180° pulse), the nuclei tend to realign themselves over an equal interval, and will only subsequently start to relax towards a random lateral orientation. The observed transverse relaxation signal between the 90° and 180° pulses and after the 180° pulse is know as spin echo. This technique is less sensitive to any inhomogeneities in

the applied magnetic field and variations in the phase orientation of nuclei in the slice of tissue selected. A succession of 180° pulses may be applied at equal time intervals in order to realign the transverse spin components and sample the resulting echoes. In this manner, the signal-to-noise ratio is increased, and is limited only by the time permitted to image a slice of the body. The rotation of the excitation pulses through 180° or 360° in a plane perpendicular to the magnetic field gradient, yields a series of relaxation projections from which an image of the (proton) distribution in the slice selected can be reconstructed.

MRI has three significant advantages as a measurement technique for body composition over X-ray. There is no radiation dose, so that repeated measurements are not limited by this factor. Secondly, the contrast between different soft tissues may be enhanced by the pulse sequence and sampling intervals with MRI, utilizing the chemical shifts of the Larmor frequency, while the contrast with X-ray CT only depends on differences of attenuation of the X-ray beam through these tissues. Thirdly, using MR spectroscopy, the abundance of various metabolites can be studied, such as $^{31}P$ in muscles and $^{13}C$ labelled glycogen in the muscles and liver.

*Dual-energy X-ray absorptiometry*

The attenuation of a beam of gamma rays through bones of the spine and femur has been used to measure bone density at these sites, and the relationship between these measurements and the skeletal density has been assumed in estimating total-body skeletal mass. Attenuation of the gamma ray beam by the surrounding soft tissue was assumed to be the same as a similar thickness of water, and usually for the purpose of maintaining a constant thickness of soft tissue, the forearm was immersed in a waterbath. However, measurements of bone density at certain sites are not necessarily representative of bone density in the whole skeleton. Consequently, whole-body skeletal measurements using radionuclide sources ($^{153}Gd$) were undertaken, measuring the attenuation of gamma rays at two energies. The two energies are attenuated to different degrees by the intervening soft tissue and bone between the source and radiation detector, and the ratios of the transmitted intensities to the intensities at each energy in the incident beam are used to deduce the amount of bone and soft tissue along the ray path. The source-detector system is moved in a rectilinear scan across the whole of the body of the supine subject, and the matrix of the attenuation ratio data is used to compute the total-body mass of soft tissue and bone. More recently, X-ray sources have replaced radionuclide sources, since the former are capable of a much higher output (and consequently, more precise measurements, due to improved counting statistics), and the latter need periodic replacement due to decay of the radioisotope. The dual-energy X-ray beam is achieved either by switching the energizing voltage across the X-ray tube between two values (40 and /0 or 100 kV) or by using a cerium filter in

the X-ray beam which absorbs X-ray photons preferentially outside the two energy bands.

This technique permits whole-body or partial-body analysis to determine local variations in bone mineral density. The precision of estimating bone mineral mass is better than 1%, but the reproducibility of the estimate of lean and fat mass is around 0.8 and 1.0 kg, respectively. The bone mineral density at known sites of skeletal weakness in osteoporosis, at the neck of the femur and in the lumbar vertebrae, can be measured accurately (< 2%). The poorer reproducibility and accuracy in the estimation of the proportion of fat and lean soft tissue is due to the small differences between the mass attenuation coefficients of these tissues (respectively, 0.0181 and 0.0182 $m^2/kg^{-1}$ at 80 kV). DEXA represents a significant advance in measurement techniques compared to early methods such as whole-body hydrodensitometry, since it is applicable in a clinical situation and can differentiate lean and fat tissue with greater accuracy and precision. It is presently an area of great interest concerning the accurate determination of bone mineral and two soft-tissue components, particularly in obese subjects. Large masses of (adipose) soft tissue have been found to impair the accuracy of the determination of bone mineral density. However, DEXA cannot distinguish between water and protein components of lean soft tissue. The radiation dose is small (1 μSv) so ethical approval is easily obtained.

Evaluating regional differences in the distribution of body fats is important because these are reliable predictors of the predisposition to metabolic complications, with android fat being more predictive than distribution to the gluteal-femoral area (gynoid fat). An increase in the percentage of fat in the neck produces an upper airway obstruction and consequently OSAS, for this reason it is important to know this percentage and, for this, we can use DEXA.

DEXA performed with a total body scanner (model QDR-4500 Hologic) allows body measurements to be divided into areas corresponding to neck, arms, legs, and trunk. The proportion of android and gynoid fat were then both expressed as a percentage of total fat.

DEXA is regarded as a ‘gold standard’ because it includes the following characteristics:

- sensitivity
- non-invasiveness
- quickness
- elevated reproductivity
- inexpensiveness

*Bioelectrical impedance analysis*

The aqueous component of the human body is able to conduct electricity due to dissolved electrolytes, whereas fat and bone are relatively non-conductive. This offers the possibility of being able to differentiate lean soft tissue from fat and bone, using measurements of tissue electrical impedance. BIA is a non-invasive, low-risk procedure for the patient. It can give immediate results, which

are useful in a clinical situation, whereas methods such as isotopic dilution (to measure TBW or extracellular fluid (ECF)) involve lengthy laboratory procedures. Much work has been carried out to relate the electrical impedance or conductivity of the human body to FFM, TBW, and intracellular and extracellular fluid compartments. Measurements of bioelectrical impedance are typically performed with four electrodes attached to the extremities of the body, two attached to the wrist, and two to the ankle. A small constant alternating current (800 μA at 50 kHz) is passed between the outermost pair of electrodes. The voltage drop across the body is measured between the inner pair of electrodes and, from this, the impedance of the body can be derived. In general, if the body is modelled as a cylindrical conductor and the resistive component is considered to dominate the impedance, for a cylindrical conductor of length L and area of cross-section A, the impedance is given by

$$Z = rL/A = rL^2/V$$

where V = AL, the volume of the conductor, and r is the resistivity of the conductor. From this equation, the volume of the conductive portion (FFM or TBW) of the human body is given by

$$\text{volume of the conductor} = \text{constant} \times \text{height}^2/\text{impedance}$$

where height has been taken to be a measure of length.

However, the body is not a cylindrical conductor. The long narrow sections of the conductive path between the electrodes, such as the arms and lower legs, contribute most to the observed impedance, while the torso and thighs, where most body mass is found, contribute at most 15%. This makes the technique insensitive to small changes of fluid in the torso, and very sensitive to the positioning of the electrodes on the wrist and ankle of the subject.

The electrical properties of whole-body impedance are modelled by an extracellular resistance ($R_e$) in parallel with intracellular impedance, comprising a series combination of an intracellular resistance ($R_i$) and cell membrane capacitance (C). In reality, the cell membranes are 'leaky' with a small amount of ionic conduction across them, and this is represented in the model by a parallel resistor ($R_m$) across the capacitor. The resistance and reactance of the combination at any frequency (f) is given by

$$R = R_e \{( R_m + R_i) (R_m + R_i + R_e) + (2\pi d f C R_m)^2 R_i(R_i+R_e)\}/D$$
$$X = 2\pi f C R_e^2 R_m^2/D$$

where

$$D = \{( R_m+R_i+R_e)^2 + (2\pi f C R_m(R_i+R_e))^2\}$$

and the impedance Z = R-i X, i = $\sqrt{(-1)}$.

The measurements are not possible at $f = 0$ and $f = \infty$, the impedance limits have to be derived by extrapolation. Changes in the fluid space of renal dialysis patients during dialysis or artificially induced by diuretics, and the change of impedance, are well-correlated with the volumes of fluid lost. Nevertheless, the geometric factors mentioned previously limit the value of this technique. Sectional impedance measurements may be carried out in which the impedance-sensing electrodes are positioned at the wrist and shoulder, at the shoulder and hip, and at the hip and ankle, in order to determine the magnitude of the respective contributions to the overall impedance by the arm, torso, and leg. In the course of such measurements, the current injection electrodes should be maintained attached to the wrist and ankle, so that the regional current density remains unchanged. Changes of fluid status in the torso are best observed with electrodes attached to the shoulder and hip.

*Electromagnetic induction*

Electromagnetic induction offers the possibility of a safe, rapid, non-invasive, non-contact, and potentially widely available method for measuring the water content of a body. A time-varying electromagnetic field will induce eddy currents in a conductive medium such as the human body, which in turn can produce a change in the impedance of the coil producing the electromagnetic field. This change of impedance may be related to the volume of body fluid (TBW) or FFM. The subject is inserted into the core of a large solenoid, whose impedance is consequently changed. This was the operating principle of a patented apparatus called TOBEC (total-body electrical conductivity), used to measure the lean and fat content of meat packages and of live and slaughtered farm animals. Early measurements of human subjects showed a reasonable correlation between the impedance change (of the solenoid) and TBW and FFM. A refinement of this technique allowed multiple impedance measurements as the subject was traversed through the solenoid, with the impedance change as a function of the subject's position being Fourier analyzed in order to derive better correlations with FFM and TBW.

## Treatment

The basic treatment of overweight and obese patients requires a comprehensive approach involving diet and nutrition, regular physical activity, and behavioral change, with the emphasis being on long-term weight management, rather than on short-term extreme weight. Range of normality is of value for studying trends in disease processes and for monitoring the response to treatment. Body composition data may influence the choice of the most appropriate treatment for wasting illnesses, sepsis, trauma, renal failure, and nutritional disorders.

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# A STATISTICAL INDEX TO DETECT POTENTIALLY OBESE PEOPLE*

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Overweight and obesity represent important public health issues in the general Italian population. The 1990-1991 Italian National Health Survey pointed out that 31.6% and 6.5% of people are overweight and obese, respectively.[1]

It has often been recognized that the prevalence of these conditions is related to the general habits of the population, even though their precise influence is not completely clear.[2,3]

In order to cope with the multivariate and complicated nature of the problem, a discriminant analysis was conducted.[4] Given a set of explanatory variables (qualitative or quantitative) related to a categorical one, this discriminant analysis allowed a decision rule to be defined that classified people according to the values of their predictors.

Based on the discriminant power of the explanatory variables, an index was developed that allocated people to different BMI classes, according to their biological (height, gender, age), social (marital status, geographic area, family size, educational level), economic (professional condition), and dietary predictors.

Such an index could be useful for estimating *a priori* the number of people at risk of becoming obese, and for targeting preventive interventions.

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*Surgery for Snoring and Obstructive Sleep Apnea Syndrome, p. 127*
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# FOOD CONSUMPTION PATTERN OF OVERWEIGHT SUBJECTS

## Preliminary results from the INN-CA Study 1995*

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The INN-CA Study 1995 was conducted by the Istituto Nazionale della Nutrizione (INN) to survey the food behavior of the Italian population. The random sample studied included 1200 households (about 3600 individuals) stratified according to the main geographical areas (northwest, northeast, center and south).

The daily food intake of underweight (BMI < 18.5), normoweight (BMI 18.5-25) and overweight (BMI > 25) people aged over 18 years was analyzed in order to explore possible behavioral differences between the three BMI classes. Single food items surveyed were aggregated into 19 food groups. The comparative analysis between overweights and normoweights led to the following results:

Overweight subjects showed a higher intake of cereal products (+9.7%), vegetables (+7.2%), green vegetables (+13.5%), legumes (+26.7%), fruit (+7.0%), meat (+11.9%), fish products (+13.1%), eggs (+4.2%), cheese (+5.7%), oil and fats (+4.4%), alcoholic beverages (+31.7%), and miscellaneous (+4.7%). Intake was lower for milk (-11.5%), yoghurt (-46.3%), sugar and sweets (-19.8%), non-alcoholic beverages (-10.4%), water (-3.2%), coffee, tea, etc. (-3.4%), and ready-to-eat dishes (-1.0%).

The 'dieting' condition seems to affect the results. In fact, a higher intake of vegetables and fish products is mainly seen in overweight subjects following a weight-reducing diet (dieters (D); 27.1%), while a higher intake of high energy density foods such as meat, eggs, cheese, oil and fats, and alcoholic beverages is mainly seen in non-dieting overweight subjects (ND) (72.9%). The same comparison carried out for the lower values of intake provided the following results: a lower consumption of milk and sugar and sweets is mainly seen in D, while less yoghurt and water is consumed by ND. For four classes of food: non-alcoholic beverages, alcoholic beverages, ready-to-eat dishes, and miscellaneous, the opposite results were obtained (Table 1).

*Table 1.* Differences seen between non-dieters and dieters in percentage

| *Food group* | *Total difference* | *Non-dieters* | *Dieters* |
|---|---|---|---|
| Non-alcoholic beverages | -10.4 | + 3.5% | -48.2 |
| Alcoholic beverages | +31.7 | +44.5 | -3.0 |
| Ready-to-eat dishes | -1.0 | +9.2 | -28.6 |
| Miscellaneous | +4.7 | +9.0 | -6.8 |

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Apart from the greatest difference seen in non-alcoholic beverages, dieters also show a big difference in ready-to-eat dishes, *i.e.*, composite dishes that are difficult to split up into single ingredients without the recipe, which is only obtainable for meals prepared at home. For this reason, most ready-to-eat dishes are consumed outside the home, and dieters tend to avoid this habit.

# THE DISTRIBUTION OF BODY MASS INDEX IN AN ITALIAN SAMPLE

## Results from the INN-CA Study 1995*

A. D'Amicis, A. Turrini, P. D'Acapito, D. Perrone and F. Silvi

*Istituto Nazionale della Nutrizione, Rome, Italy*

In 1995, a large-scale study, known as the INN-CA Study 1995, was carried out by the Istituto Nazionale della Nutrizione (INN) to survey the food behavior of the Italian population. The random sample studied was represented by 3600 individuals from 1200 households stratified according to the main geographical areas (northwest, northeast, center and south). Each individual was asked to measure his/her own weight on a bench scale and his/her height was measured with the back against the wall, using a square tape meter.

The distribution of the sample by body mass index (BMI) was analyzed in order to ascertain the prevalence of subjects in each BMI class and to identify the major features of underweight (BMI < 18.5), normoweight (BMI 18.5-25) and overweight (BMI > 25) in persons aged over 18 years. The percentage of subjects in each of the three classes was 4.9%, 64.4% and 30.7%, respectively. In the northern regions, the prevalence of normoweight was higher than in central and southern areas (northwest, 29.9%; northeast, 22.5%; center 34.6%; south, 34.2%). According to gender, underweight and normoweight are seen more frequently in females (7.6%), while males present with the highest percentage of overweight (40.9%). Age also influences distribution of the BMI classes: the older the subjects are, the higher the percentage of overweight. Overweight is more frequent among married persons (39.7%) and widows (42.3%). Moreover, when considering the dichotomic variable 'single', the percentage of overweight in people living alone is 25.0%, compared to 31.3% of people living with other persons. Overweight is mainly present in subjects who are the head of the family (44.9%). The authors also took educational level into consideration: persons with a low degree of education have the highest BMI values: in persons with no qualifications or with a primary school certificate only, the prevalence of overweight rose to more than 50%; the lowest value was observed in persons with a university degree (24.5%). Demographic aspects were also taken into account: overweight individuals are more often present in the smallest (33.7%) and largest (34.0%) towns.

These findings verify results seen in Italy and various other western countries, confirming the finding that overweight and obesity are more often present in less-privileged social classes.

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# FOOD CONSUMPTION AND OBESITY IN ITALY

## Recent trends*

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The relationship between body mass index (BMI) and the dietary habits of the population is not completely clear, since the effect of many other factors (both genetically and environmentally determined) help to obscure this. Nevertheless, the joint analysis of recent trends in obesity and food consumption can help to gain a better understanding of this association.

During the last decade, the body measurements of adult Italians have seen a slight modification, in that BMI has increased by an average of 0.5 $kg/m^2$ in males and has decreased by 0.1 $kg/m^2$ in females. Deeper insight into this rather small level of change can be obtained from three large-scale epidemiological studies conducted in Italy in the 1990s, which supplied data on the mean height and weight of the population by gender and geographical area.[1-3] These studies showed that 46% and 38% of males and females, respectively, in Italy is overweight or obese, with persons living in the southern part of Italy and coming from the middle-aged classes, being more obese than the others. Data also highlighted that overweight is becoming an increasingly worrying health problem in males, while the prevalence of underweight in females is growing (about 15-20% of the young female population).

With regard to dietary habits, data processed by the National Institute of Statistics showed that food availability underwent a strong modification in Italy between the 1980s and 1990s. The quality and quantity of food ingested has changed, mainly in composition. The use of wheat, sugar, wine, milk and butter declined, while vegetables, eggs and poultry showed a slight increase, and rice, fish, fresh fruit, seed oils, pork and meats other than red varieties, a larger one.

However, this trend towards an increase in fat intake at the expense of carbohydrates and a slow divergence from the healthy Mediterranean Italian diet has slowed down recently and has even halted, as can be seen from data recorded after 1990, and from the preliminary results of surveys conducted by the National Institute of Nutrition between 1993 and 1995.

These findings are apparently in contrast to the explosion in the prevalence of overweight exhibited in the same years, but this can be explained by the clear and continuing reduction in the level of physical activity seen in the population.

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# A BODY WEIGHT CONTROL PROTOCOL FOR OBSTRUCTIVE SLEEP APNEA SYNDROME PATIENTS*

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The prevalence of sleep apnea syndrome (OSAS) has been estimated to be between 4% and 8% in the adult population. CPAP is considered to be the primary treatment for apnea.[1] However, compliance with CPAP is not very high, even after acclimatization.[2] Thus, it is important to consider adjunctive behavioral treatments in order to increase the efficacy of and/or compliance with CPAP.

The association between obstructive sleep apnea and obesity is well known.[3,4] A significant, positive relationship has also been reported between body weight and CPAP.[5] These data, as well as other evidence, suggest that the treatment of OSAS disturbances would benefit from combining CPAP and body weight control.

The aim of the present report is to present an individual treatment protocol for reducing and maintaining body weight. This protocol combines education, behavioral and cognitive strategies (*e.g.*, stimulus and behavior control procedures, self-reinforcement, cognitive restructuring, etc.) aimed at changing eating habits and preventing lapses and relapses, and at helping OSA patients adopt a life style that may warrant the maintenance of a reasonable body weight.

Cognitive-behavioral programs for reducing and maintaining body weight have been shown to be effective in both short- and long-term follow-up studies.[6]

Based on a review of the literature, the following issues will be addressed: can body weight control be substituted for CPAP when OSAS is not severe? Should negative attitudes toward CPAP and/or surgery be used as motivating factors for body weight control? Can the reduction of body weight increase the compliance to CPAP?

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# SOFT PALATAL DYNAMICS, HISTOLOGY, AND BODY FAT DISTRIBUTION IN PATIENTS WITH PARTIAL UPPER AIRWAY OBSTRUCTION*

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This study assesses the upper airway dynamics, soft palatal morphology, and body fat distribution of patients operated on for partial upper airway obstruction.

The upper airway dynamics were studied preoperatively using the digital fluoroscopy method. Laser-assisted uvulo-palato pharyngoplasty was carried out in 22 patients suffering from a mild to moderate form of upper airway obstruction, as verified by sleep mattress examination and pulse oximetry. The histology of the tissue removed was analyzed morphometrically and the degree and distribution of body fat in the patients determined.

The results indicate that dynamic collapsibility correlated with the degree of apnea disease. The percentages of fat and loose connective tissue in the soft palate correlated well with the collapsibility of the nasopharynx and the severity of the disease, but not with the distribution of body fat in these patients.

The development of obstructive sleep apnea syndrome is a gradual, subtle process, closely related to metabolic and circulatory disturbances. These results support the theory that, to start with, factors other that those purely related to obesity may influence the progress of sleep apnea disease.

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# OBSTRUCTIVE SLEEP APNEA SYNDROME AND SYSTEMIC DISEASES

# NEUROGENIC FACTORS

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## Introduction

The pathophysiology of obstructive sleep apnea and hypoapnea syndrome (OSAHS) has been studied extensively over the past three decades. Nevertheless, a clear understanding of its complex mechanisms is still lacking.

Obstructive sleep apnea is a syndrome characterized by recurrent collapse of the pharyngeal airway during sleep. Therefore, there is a clear correlation between sleep and the obstructive episodes. However, what is not clear enough is how, in such a remarkable way, sleep can influence pharyngeal muscles functions, and what impact central control has on upper airway (UA) collapsibility.

Many studies have shown a close correlation between craniofacial dysmorphism, obesity, hypertrophy of pharyngeal soft tissues, and obstructive sleep apnea. Even moderate anatomical changes of the UA can alter the complex physiology of intrapharyngeal pressure and modulate the activity of the related dilator muscles.

However, anatomical variations cannot be the only 'culprit' for all obstructive episodes, since there are subjects with equally narrow UAs who do not have OSAHS. This strongly suggests that functional factors may be important in the pathogenesis of OSAHS.[1] Several authors have focused their attention on the role played by neurogenic mechanisms in obstructive sleep apnea. In order to understand the nature of these relationships, we will review some basic concepts of pharyngeal anatomy and physiology.

## Pharyngeal anatomy

The upper airways are comprised of the nose, nasopharynx, oropharynx, and hypopharynx. OSAHS is a multilevel disease in which the obstructive site var-

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ies amongst patients, but is generally located behind the uvula and the soft palate (oropharynx), behind the tongue base (hypopharynx), or at both levels (orapharynx-hypopharynx).[2,3]

Aging, obesity and anatomical anomalies such as retrognathia, maxillary or mandibular hypoplasia, hypertrophy and redundancy of the soft palate and uvula, and hypertrophy of the palatine tonsils, influence the size of the UA.

The pharynx is a complex and versatile organ which controls respiration, phonation, and swallowing. Accordingly, the anatomy, physiology, and nervous control of the pharynx cater for these multiple needs. The pharynx has to be compliant enough to guide food into the esophagus, but at the same time, sufficiently rigid to maintain UA patency. Unlike other adjacent structures (nose, larynx, and trachea), the pharyngeal lumen lacks the rigid support provided by bones and cartilages, with the exception of the hyoid bone. Thus, the pharyngeal dilator muscles play a fundamental role in maintaining UA patency (Fig. 1). The dilators include the tensor palatini, levator palatini, genioglossus, geniohyoid and medial pterygoid. These muscles move the soft palate, mandible, tongue, and hyoid bone anteriorly, stiffening and enlarging the pharyngeal lu-

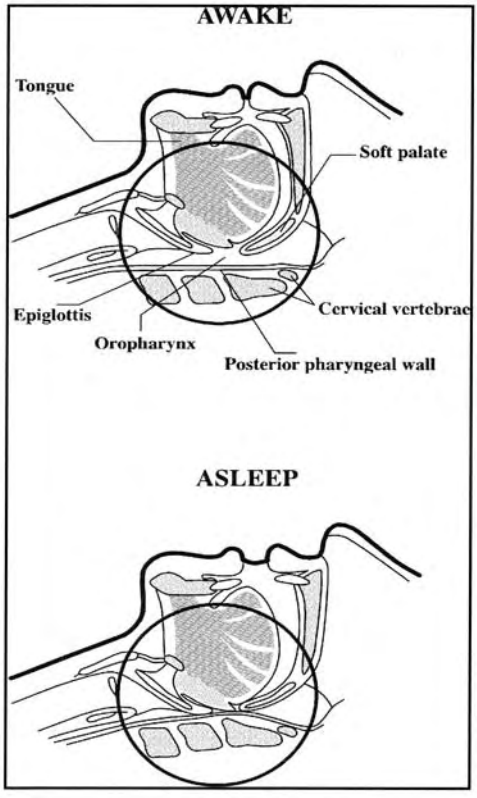


*Fig. 1.* During sleep, the reduced dilator tone contributes to UA collapsibility. (Adapted from White[12] by courtesy of *Thorax*.)

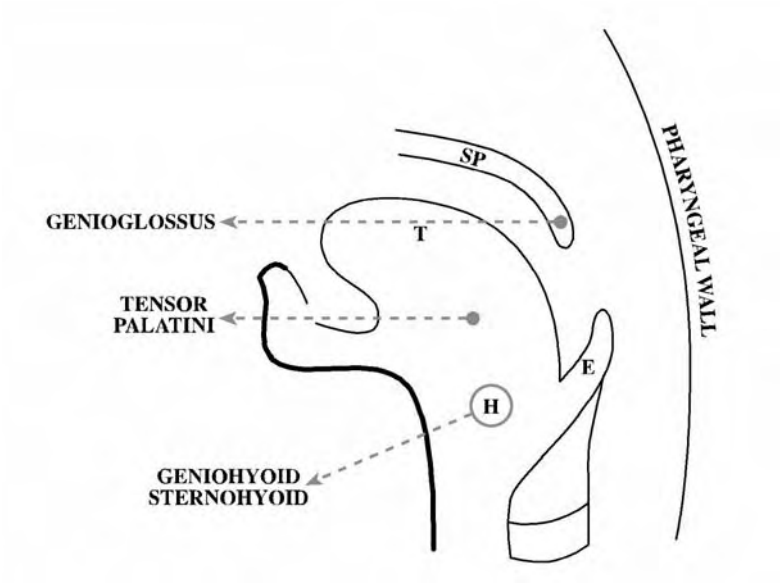


*Fig. 2.* Principal UA dilator muscles. The arrows show the direction of their action. The direction of the lower arrow represents the combined action of both muscles. (Adapted from Kuna and Remmers[24] by courtesy of the publisher.)

men (Fig. 2).[4,5] Their action results in a complex balance of opening and occluding forces, which are also influenced by the intraluminal pressure of the pharynx.

The diaphragm expands the thoracic volume, thereby creating negative intrathoracic pressure. This leads to a transmural pressure gradient that tends to collapse the airway. Moreover, gravity in the supine position pulls the tongue and the anterior pharyngeal walls backward, further decreasing UA lumen. The pharyngeal dilator muscles are the main opponents to these collapsing forces and therefore their function is crucial.

The geometry of the UA also plays an important role as it determines airflow pattern. A high flow rate in a narrow lumen will cause a turbulent flow, and the Bernoulli forces will lead to airway obstruction.

## Pharyngeal physiology

The activity of the pharyngeal dilator muscles is dependent on numerous variables, including changes in blood gases (reduced $PCO_2$ and increased $PO_2$), proprioceptive inputs, changes in consciousness levels, vagal reflexes, and intrapharyngeal pressure.[6-9] Pharyngeal and laryngeal pressure receptors seem to be sensitive to changes in intraluminal pressure (Fig. 3).[8,9]

Pharyngeal dilating muscles show tonic basal activity and rhythmic activa-

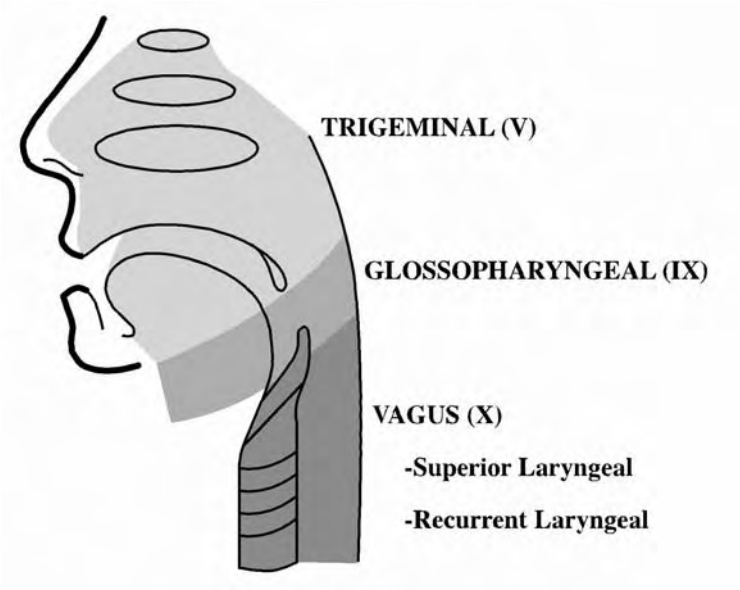


*Fig. 3.* Pharyngeal and laryngeal receptors are thought to be sensitive to increasing levels of intraluminal pressure.

tion during inspiration. The size of the UA is largely determined by changes in equilibrium between dilator muscles, maintaining pharyngeal patency, and intraluminal pharyngeal pressure, which tends to make the airway collapse.

During sleep, most of the dilator muscles show a marked reduction of their contractility.[4,11,12] As a result of this, increased inspiratory resistance develops in the UA, which ultimately causes partial or total occlusion. In the presence of anatomical and physiological anomalies, the size of the UA may be reduced up to a critical level beyond which the activity of the dilators is either limited or insufficient to maintain intraluminal patency.[13]

An individual with a large pharyngeal airway may be minimally dependent on dilator muscles activity, which, on the other hand, may become fundamental with anatomically narrower airways.[14,15] As mentioned above, this condition, although suitable for the majority of OSAHS subjects, cannot be seen as the only factor in the pathogenesis of all obstructive sleep apneas, since a number of OSAHS patients have normal craniofacial skeletal patterns and pharyngeal structures. It therefore appears that anatomical factors alone do not entirely explain the complete etiology of the syndrome.

## Neurogenic mechanisms

Partial or total occlusion of the UAs is closely related to an increase of negative intrathoracic pressure during inspiration that can greatly influence pharyn-

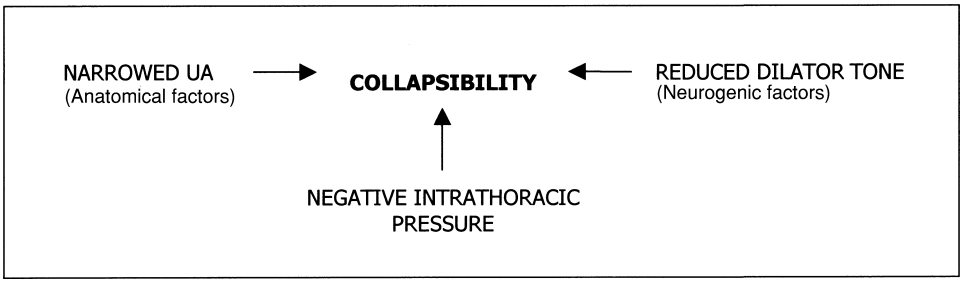


*Fig. 4.* Factors contributing to UA collapsibility during sleep.

geal collapsibility. In addition, sleep reduces dilator tone more than diaphragmatic contractility. This results in a negative intrathoracic pressure, which is not balanced by the UA dilators activity. Consequently, an abnormal resistance develops in the pharyngeal lumen, which is responsible for the obstructive episodes.

Figure 4 proposes the role played in the pathogenesis of OSAHS by the two major mechanisms discussed in the previous sections, the intraluminal negative pharyngeal pressure generated by the intrathoracic inspiratory effort, and the anatomical abnormalities. The third factor illustrated in the scheme is the influence of neurogenic factors on the activity of the pharyngeal dilator muscles.

Sleep is a powerful inductor of apneas and its action differs between morpheic stages. Ventilation patterns vary among sleep phases, together with the progressive transition from wakefulness to stage 2. During sleep, the set point of ventilatory control (the point at which the respiratory system is stimulated) is higher than during wakefulness.[16] Ventilatory drive decreases from wakefulness to sleep and an arousal will result in an increase of respiratory volumes.[17] For this reason, the alternation between drowsiness and arousal at sleep onset causes breathing instability; this is expressed by oscillation from hyperventilation to hypoventilation, resulting in periodic breathing. The frequency of this periodic respiration, observed in 40-80% of normal subjects, varies from 60-90 seconds, and apnea duration lasts between ten and 40 seconds.[18] When the level of hypocapnia, secondary to the hyperventilating phase, falls below a given threshold (the apneic threshold), the respiratory drive is interrupted. As a result, an apneic event develops (Fig. 5).[19-21] The apneic threshold is higher during sleep than during wakefulness and therefore apneic episodes occur more frequently during sleep. Moreover, hypoxia and hypercapnia, strictly related to the apneic phase, are strong arousal stimuli,[22] thereby increasing the 'unsteadiness' of the system. This respiratory instability will raise UA resistance and favor pharyngeal collapse. In normal subjects, as sleep deepens, breathing instability is reduced and the apneic events become rare. This close relationship between sleep and ventilatory drive could explain central apnea during periodic breathing, but is probably important in the pathogenesis of OSAHS as well.

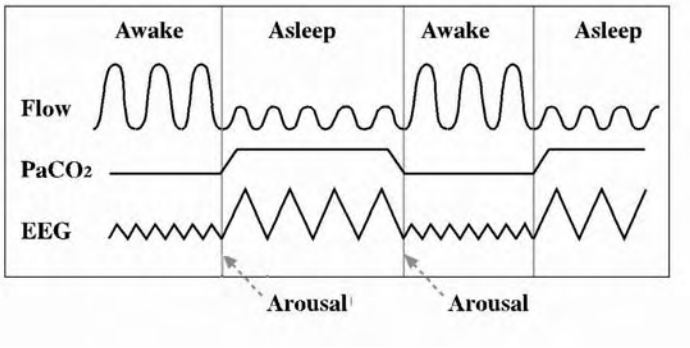


*Fig. 5.* Ventilation instability is closely related to periodic resetting of the central $PaCO_2$ receptors and to the wakefulness-sleep cycle.

In fact, several observations in OSAHS subjects, snorers, and normal individuals during sleep, have shown a clear correlation between changes in UA patency and shifts in the sleep-wakefulness cycle.[24] UA dilator tone is reduced during sleep in both normal subjects and apnea patients. These muscles behave in a variety of ways. In general terms, we can distinguish *phasic muscles*, such as the genioglossus, and *tonic muscles*, such as the tensor palatini. The former have a peak contraction during inspiration (Fig. 6) while the latter have homogeneous activity during the respiratory cycle and maintain airway patency throughout inspiration and expiration.[12] Phasic and tonic neural stimuli reach the pharyngeal muscles modifying their tone. Hypoglossal motoneurones, innervating the genioglossus, receive important inputs from respiratory neurons and may be influenced by sleep mechanisms.[25] It has been shown that, during wakefulness, the genioglossus muscle in OSAHS patients performs at a higher level of activity compared to normal subjects (Fig. 7).[15] The muscle hypertone is a reflection of the increased resistance in the UA generated by intrathoracic negative pressure. Thus, the UA dilators maintain intraluminal patency at the expense of greater activity. This adaptive mechanism partially compensates for the anatomically small UA seen in OSAHS. Therefore, it is a combination of the normal decrement in muscle tone and the progressive loss of muscle contraction, counteracting the elevated intrapharyngeal pressure, that most likely contributes to OSAHS pathogenesis.[12]

Moreover, there is some evidence that pharyngeal dilator muscles undergo secondary changes in structure as a direct consequence of their increased activity level.[26] Several studies have suggested that local muscular abnormalities, including neurogenic lesions, could be contributory factors in the etiology of OSAHS. Biopsies of pharyngeal dilators have shown morphological abnormalities (increased number of hypertrophied and atrophied fibers) in snorers and apnea patients, compared with normal individuals.[27-29] The hypothesis of a progressive local neurogenic lesion could support the theory that there is a progressive heavy snorers disease[30] that, at a later stage, determines the in-

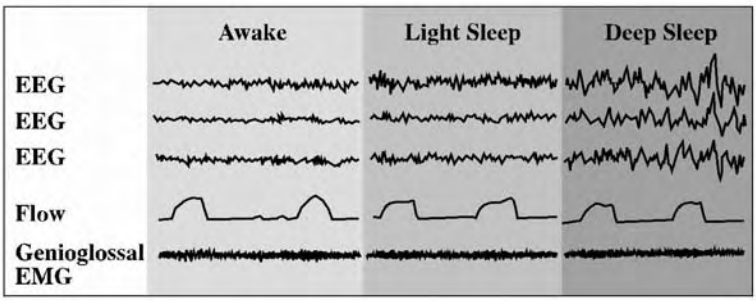


*Fig. 6.* The phasic activity of the genioglossus muscle with the peak contraction during inspiration.

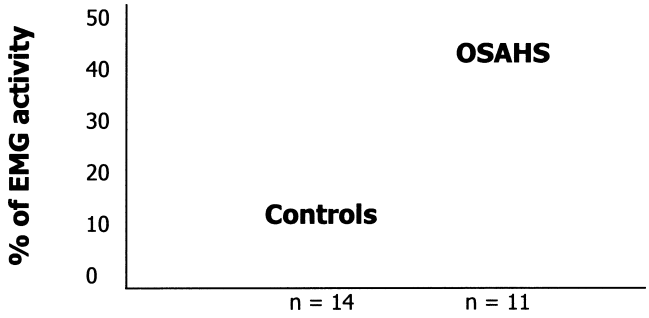


*Fig. 7.* Maximal genioglossal phasic activity in apnea patients and control group during wakefulness. Note how the mean genioglossal activity is much higher in the OSAHS group. (Adapted from Mezzanotte *et al.*[15] by courtesy of the *Journal of Clinical Investigation*.)

creased collapsibility and obstruction of the UA seen in OSAHS. However, it still remains unknown whether the histological abnormalities precede the syndrome in predisposed subjects or represent a consequence of the obstructive episodes.

These functional mechanisms acquire even more importance in view of studies conducted on subjects with sleep-disordered breathing, using magnetic resonance proton spectroscopy, which found increased thickness of the lateral pharyngeal walls which could not be attributed to increased fat infiltration or edema.[31]

A typical feature of OSAHS is represented by UA obstructions between periods of arousals that show a 20-40 seconds cyclic pattern. Overall, this periodism resembles a physiological EEG rhythm, known as the cyclic alternating pattern (CAP), consisting of transient arousals that periodically interrupt NREM sleep stages.[32] This is a condition of *arousal instability* oscillating between a greater arousal level (phase A) and a lesser arousal level (phase B). Data suggest that sleep fragmentation in OSAHS is significantly associated with an increase in phase A rate. This theory points to the implication of phase B as a vulnerable background for UA collapsibility and for the decrement of ventilatory drive.

Progression into the stable stages of sleep (III and IV) greatly reduces the frequency of UA obstructions. This EEG periodism is thought to be modulated by peripheral factors that contribute to integrate different information into a closed network.[33]

However, there is still no evidence as to which central mechanisms are involved in the regulation of respiratory drive to the UA muscles in sleep apnea patients, or which neurotransmitters are involved.

## Conclusions

Obstructive sleep apnea is a sleep-induced syndrome and therefore the pronounced influence of central sleep mechanisms on UA muscle activity is not in doubt. The existence of a natural electroencephalographic periodic rhythm, between arousals and sleep, suggests that OSAHS 'periodism' is under strong central control. Obstructive episodes appear to be tightly associated with arousal and ventilatory instability, which are not present in the deep and stable stages of sleep.

The pathogenetic mechanisms of OSAHS are most likely based on a close interplay between anatomical, physiological, and neurogenic factors. This heterogeneous control of the pharyngeal caliber becomes critical during sleep when a new equilibrium (normal subjects) or disequilibrium (OSAS patients) is reached. Identification of the central neuronal mechanisms and neurotransmitters involved in the reduction of the UA dilator muscle activity during sleep is of great clinical relevance. Understanding these processes could lead to pharmacological control of airway patency and ultimately to OSAHS treatment or prevention.

## Acknowledgments

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# GASTROESOPHAGEAL REFLUX DISEASE AND OBSTRUCTIVE SLEEP APNEA SYNDROME

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## Definition

Gastroesophageal reflux disease (GERD) is the most common esophageal disease and is characterized by gastric reflux being seen with greater frequency in the esophagus, gastric material being present for a longer time, and the capacity of the defences being reduced.[1]

This type of disease is not always associated with alterations in the esophageal mucosa (esophagitis). In fact reflux can be found without esophagitis during upper endoscopy, but when pyrosis has existed for at least three months: this entity is commonly called non-erosive reflux disease (NERD). Patients with NERD have the same quality of life and require the same treatment as patients with GERD.[2]

*Key concept:* reflux is not always seen with esophagitis, however, in this case, a distinct entity known as NERD will be present.

## Pathophysiology of gastroesophageal reflux disease

The primary barrier against gastrointestinal reflux is the lower esophageal sphincter, which is located at the level of the diaphragmatic hiatus and acts as the main deterrent to the reflux.[3] Other structures that may be involved in preventing reflux are the intra-abdominal segment of the esophagus, the gastroesophageal angle, the diaphragmatic crura, and the phrenoesophageal ligament. Gastric motility also plays a role, with delayed emptying predisposing the patient to GERD. The upper esophageal sphincter mainly consists of the cricopharyngeal muscle and a small portion of the pharyngoesophageal junction, and serves as the main barrier in preventing laryngopharyngeal reflux.

Every time the intragastric pressure is higher than the lower esophageal sphinc-

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ter pressure, there can be reflux; this occurs in physiological conditions, such as after eating, or in pathological conditions, such as obesity.

The mechanisms leading to reflux are as follows:

- inappropriate transitory relaxation of the lower esophageal sphincter;
- huge increases in abdominal pressure;
- reflux of gastric acid through the esophageal sphincter.

Inappropriate transitory relaxation of the lower esophageal sphincter (LES) seems to be the most important mechanism leading to this condition, but is not the only one.[4,5] In fact, there is a new theory that seems to point to GERD: short and intermittent episodes of lower esophageal sphincter relaxation (TLESR) due to a sudden and transient reduction of LES pressure below the intragastric level. Basal LES pressure is within the normal limits. Approximately 80% of reflux episodes are due to TLESRs.

How are TLESRs initiated? The mechanism probably begins with gastric distension and pharyngeal stimulation; this leads to mechanoreceptor stimulation in the cardias and pharynx; this could stimulate the vagal nuclei in the encephalic trunk via the afferent vagal way. The consequence may be LES relaxation, diaphragm inhibition, and therefore esophageal relaxation via the efferent vagal way.

The role of hernia of the hiatus in the pathophysiology of GERD is a frequent subject of discussion.[6,7] Esophagitis results from an excessive reflux of gastric juices rather than from excessive gastric secretion.[8] The squamous epithelium of the esophagus is intolerant to repeated exposure to gastric acid for prolonged periods. Reflux symptoms become steadily more serious. The complications seen with GERD, broadly categorized as esophagitis, Barrett's metaplasia, and extra-esophageal manifestations, also become more serious.

Low-grade esophagitis can only be seen on histopathological examination. High-grade changes can be seen endoscopically as erosions and ulcerations. Peptic strictures and Barrett's metaplasia result from the response that follows ulceration.

Various risk factors are involved, the most important being alcohol intake and obesity. Other risk factors include smoking, drugs, hormones, radiation therapy, exercising, and the consumption of carbonated drinks.

## Clinical presentation

Typical symptoms are the presence of heartburn and acid regurgitation, either alone or in combination. These symptoms can occur at any time, but are most frequent in the post-prandial period or in a particular body position. Heartburn is uncommon in patients with extra-esophageal manifestations.

*Key concept:* typical esophageal symptoms are absent in most cases with extra-esophageal symptoms.

The iceberg theory: the majority of patients with GERD do not seek medical attention; many patients with mild recurrent symptoms assume that they are suffering from indigestion and do not apply for a medical prescription. Patients who develop frequent symptoms are seen by primary care physicians, and only those with chronic persistent symptoms and complaints are seen by gastroenterologists.

## Complications

Two types of complications can be encountered: esophageal and extra-esophageal.

### *Esophageal complications*

As mentioned above, the most common esophageal complication seen in GERD is esophagitis. Due to the length of time the squamous epithelium is exposed to the gastric juices, it can develop alterations such as metaplasia (Barrett's esophagus), stenosis, ulceration, and adenocarcinoma.

### *Extra-esophageal complications*

Extra-esophageal symptoms are found in the structures near the esophagus, such as the head, neck, and respiratory apparatus, and mostly occur when there are alterations in the upper esophageal sphincter, which usually serves as the main barrier for preventing laryngopharyngeal reflux. The pathophysiology of GERD in patients with gastrointestinal symptoms differs from that in patients with head and neck symptoms. Patients with gastrointestinal symptoms have esophageal dismotility and dysfunction of the LES, while patients with head and neck manifestations have dysfunction of the upper esophageal sphincter but good esophageal motility.[9] Patients with gastrointestinal symptoms usually experience esophageal reflux when they are in a supine position, while patients with extra-esophageal manifestations present with laryngopharyngeal reflux during the daytime when they are in an upright position.

The following conditions have been reported to be associated with GERD: laryngeal carcinoma, subglottic stenosis, chronic laryngitis, contact ulcer, laryngeal granuloma, cricoarytenoid fixation, intubation granuloma, laryngomalacia, pachydermia, laryngospasm, chronic cough, chronic pharyngitis, dysphagia, aerophagia, buccal burning, cervical pain, choking sensation, constant throat clearing, food being stuck in the throat, globus sensation (the most common symptom), halitosis, dysphonia, otalgia, pharyngeal tightness, and obstructive sleep apnea syndrome (OSAS).

*Key concept:* patients with extra-esophageal symptoms do not necessarily report any gastrointestinal symptoms.

The diagnostic work-up of patients presenting with symptoms of laryngopharyngeal reflux begins with a thorough history and a meticulous clinical examination. Patients with laryngopharyngeal reflux present with symptoms related to the upper aerodigestive tract. The most common symptom reported is the globus sensation. Some studies have shown that, in 23-60% of patients presenting with globus sensation, GERD is the etiological factor.[10,11]

## Gastroesophageal reflux disease and obstructive sleep apnea syndrome

A number of studies have recently described the presence of GERD in patients with OSAS.[12-14] These studies noted the coexistence of both syndromes in the same patients, and that nasal continuous positive airway pressure (nCPAP) reduced the frequency and severity of acid reflux episodes. Kerr *et al.* found that five of six patients with OSAS showed significant acid esophageal reflux on esophageal pH monitoring. and that arousals preceded reflux events.[13]

There are many possible reasons for the association between these two diseases. The same type of patient is predisposed to both conditions, with common etiological factors being obesity and alcohol intake. In addition, GERD may precipitate symptoms suggestive of OSAS, including nocturnal choking and arousal by micro-aspiration of gastric acid. Acid reflux may also cause laryngeal inflammation and edema, which, in turn, may worsen upper airway obstruction. On the other hand, OSAS has the potential to trigger acid reflux episodes. Apneic episodes during sleep are associated with continued inspiratory efforts against a closed upper airway. This results in decreased intrathoracic pressure and increased transdiaphragmatic pressure during obstructive episodes. This could trigger GERD events, particularly if relaxation of the LES coexists.

There is good evidence that GERD could be involved in the pathogenesis of arousals in patients with OSAS. However, whether this is via a vagally mediated reflex or via direct micro-aspiration has not yet been ascertained. Thus, a direct temporal or causal relationship between acid reflux and apneas still has to be ascertained. To our knowledge, there have only been a few studies in a limited number of cases.[13,15,16] Therefore, larger studies are required in order to investigate this relationship further. The effects of arousals, obstructive apneas, and sleep deprivation on GERD, and specifically on transient LES relaxation, still remain to be studied.

*Key concept:* OSAS and GERD have some important risk factors in common, such as alcohol intake and obesity.

*Hypothesis*

- GERD and OSAS are not related but coexist due to the similar predisposing factors
- GERD is a trigger factor for OSAS
- OSAS induces GERD
- GERD and OSAS make each other worse

## Diagnosis

The first step in the diagnosis is a strong clinical suspicion. The point between normality and a pathological condition is uncertain. The association between hiatal hernia and GERD is no longer considered clinically important, since 40-60% of totally asymptomatic patients have clearly demonstrable hiatal hernias. Barium esophagography is only sensitive to reflux in 20-33% of cases.

Endoscopy allows any possible damage to the esophageal mucosa to be demonstrated, and it is the gold standard for establishing any precancerous lesions.

Prolonged pH manometry has become the gold standard. The sensitivity and specificity of this technique are in the region of 100%. Normal subjects should not have an esophageal pH of less than 4 for 6.3% of the time in the upright position, 1.2% of the time in the supine position, or 4.2% of the total time.

False negative results can occur after technical probe failure or inappropriate sampling.

## Therapy

Therapy is based on many approaches, including modification of diet and lifestyle: fat decreases LES pressure and delays gastric emptying. On the other hand, protein intake increases LES pressure and should be encouraged. It is advisable to avoid chocolate, mints, carbonated drinks, caffeine, and ethanol. Stopping smoking is also recommended. Overeating should be avoided, as should lying down within three hours of eating. However, this treatment alone is not sufficient for patients with severe disease or complications.

It is better to add medications that reduce gastric acid production and enhance LES tone, while promoting gastric emptying. $H_2$ blockers effectively and safety depress acid secretion. These agents selectively inhibit stimulation of the parietal cells by histamine. They include cimetidine, ranitidine, and famotidine. Cholinergic agents have several effects. They have been shown to increase LES pressure, increase the amplitude of esophageal peristalsis, and promote gastric emptying. Available agents are bethanecol and methoclopramide.

Most importantly, the use of protonic pump inhibitors (PPI) is recommended,[15] at doses depending on the damage caused by GERD, diagnosed by means of

upper endoscopy and based on the histological grade (Table 1). The drug actually considered to be the most effective is esomeprazole. Surgical treatment should be considered when therapy with PPI is not effective.

*Table 1.*

| | *Mild esophagitis* | *Moderate-severe esophagitis* |
|---|---|---|
| *Histological grade* | *I Savary-Monnier or A-B Los Angeles* | *II-IV Savary-Monnier or C-D Los Angeles* |
| Acute phase | PPI for 2 months | PPI for 12 months |
| Maintenance | PPI at minimal effective dose | PPI at minimal effective dose |

The therapy for patients with extra-esophageal symptoms should be based on the same medications mentioned above.

*Therapy for gastroesophageal reflux disease and obstructive sleep apnea syndrome*

There are very few studies that evaluate the therapy for GERD and OSAS together, and these only include small numbers of patients. For example, one study evaluated the benefits of antireflux therapy (one month of nizatidine 300 mg/daily), and noted an apparent reduction of arousals and apnea/hypopnea index (AHI) in six OSAS patients. In the same study, it was noted that nCPAP appears to reduce GER parameters in both OSAS patients ($n = 7$) and controls ($n = 7$).[16]

## Conclusions

- The association between GERD and many pathological otorhinolaryngological conditions is well documented.
- GERD is frequently found in OSAS patients and *vice versa*.
- However, GERD and OSAS have similar risk factors and the possibility that they simply coexist should be ruled out in large epidemiological surveys.
- Therapeutic trials in a small number of patients appear to demonstrate the beneficial effect of antireflux therapy on OSAS parameters.

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# NOCTURIA: SECONDARY TO OBSTRUCTIVE SLEEP APNEA SYNDROME OR TO CERVICO-URETHRAL OBSTRUCTION?

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## Introduction

Nocturia is an extremely aspecific symptom, secondary to different pathologies not necessarily associated with disorders of the urinary tract (Table 1). The incidence of nocturia in the general population is high: in fact, 64% of subjects older than 65 years wake up for voiding at least once per night and 29% twice or three times.[1] Among patients suffering from obstructive sleep apnea syndrome (OSAS), or in chronic snorers, the incidence of nocturia is even higher, being present in 79%.[2]

The various etiopathogenetic hypotheses for nocturia in patients suffering from OSAS proposed during the last years are rather controversial because the true onset process still has to be determined. One of the most popular hypotheses asserts that, in these patients, abolition of the normal nocturnal renal circadian rhythm occurs, with an increase in diuresis, natriuresis, and creatinine clearance during sleep, compared to the standard population.[3,4] It has been

*Table 1.* Causes of nocturia

| *Urological disorders* | *Non-urological disorders* |
|---|---|
| Cervico-urethral obstruction (CUO) | Diabetes |
| Bladder functional disorders | Renal failure |
| Neurogenic bladder | Excessive consumption of liquids |
| Genito-urinary infections | Diuretics |
| Sleeping disorders | |

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proposed that atrial natriuretic peptide (ANP) is mostly responsible for the alteration in renal circadian rhythm. The high pressure produced in the pulmonary artery, and the persistent and repetitive generation of high negative intrathoracic pressure during the apnea periods, could cause cardiac stretching sufficient to stimulate the release of ANP.[5-7] However, according to another hypothesis, nocturia could also depend on increased intra-abdominal pressure, very often associated with obesity, due to obstruction of the respiratory tract.[8] Since nocturia is often considered to be a 'commonplace' symptom secondary to a urinary pathology of an obstructive type, in our urological experience, we have noted that the night awakening for voiding is not necessarily due to a urinary disorder, but rather to increasingly superficial sleeping, to years of habit, or even to nocturnal polyuria.

The goal of our study was to assess whether nocturia in OSAS patients or chronic snorers could be associated with urological disorders still underestimated or underrated by the patient himself, by checking in how many of these patients nocturia is really attributable to the nocturnal respiratory pathology when it could also be the result of micturitional disorders, often occurring slowly, secondary to cervico-urethral obstruction (CUO).

## Material and methods

Since 1998 we have been studying a group of 52 male patients, aged between 40 and 71 years (mean age, 61 years), suffering from OSAS (34 patients) or chronic snoring (18 patients), who at least had constant nocturia with a frequency of one to two episodes per night (43 patients), or severe nocturia with more than three episodes per night (nine patients).

Patients with occasional nocturia, those suffering from diabetes or chronic renal insufficiency, those under pharmacological treatment (diuretics), and patients with urological diseases previously diagnosed or treated, were excluded from the study.

During an ENT examination, a urological questionnaire, the International Prostate Symptom Score (I-PSS), compiled in numerical terms (range, 5-35), was submitted to the selected patients suffering from nocturia. This provided a subjective evaluation of the micturitional habits of the patients and of how much the micturitional disorder affected their quality of life (QL) (range, 0-6). Patients with a high symptomatological score (>15) on the I-PSS underwent a urological examination and, when there were clinically significant objective findings, a urodynamic examination was recommended. Such an examination provides us with information on the presence of a possible CUO or functional sphincter-vesical alterations, by measurement of urination speed (uroflowmetry) and evaluation of intravesical pressure during the filling phase and during urination (cystomanometry, pressure-flow study).

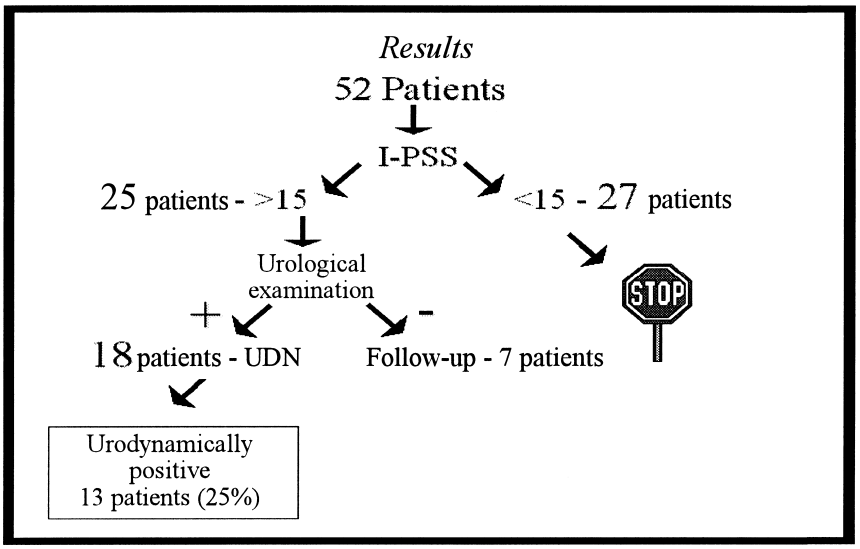


*Fig. 1.*

## Results

Of the 52 nocturia patients suffering from OSAS and chronic snorers who completed the I-PSS questionnaire, no further examinations were performed in 27 cases since they had an I-PSS lower than 15. The 25 patients with an I-PSS higher than 15 underwent urological examination, after which, 18 of them who showed a significant clinical pattern of urinary obstruction, underwent urodynamic examination. Thirteen patients in this latter group showed an altered urodynamic pattern: 11 had CUO (70% with Schaefer >3; n.v.: <2); two vesical instability.

Sixty percent of the subjects had a 'QL' score of >2 (range 0-6; n.v.: <2); 50% of them presented with a maximum flow lower than 12 ml/sec (n.v. >15 ml/sec). Only one patient had severe nocturia (three to four times per night). Of the 13 patients positive to the urodynamic tests, nine were suffering from OSAS and four were symptomatic snorers (Fig. 1).

## Discussion

From our study, some data emerged which, even if not substantiated by a very large study group, could be indicative of certain aspects.

We noted how nocturia only presented in a more severe way (three to four times per night) in patients suffering from OSAS, or in symptomatic snorers. Likewise, on the I-PSS test, this same group showed the lowest rate of micturitional disorders. On the other hand, the patients who showed moderate nocturia (once

or twice per night) answered the I-PSS test by complaining of a greater frequency of diurnal nuisance. In particular in this group, the presence of micturitional disorders was demonstrated to be urodynamically significant.

From this we can guess that, when nocturia is more intense, it is more probably due to the OSAS only; on the other hand, when it is present but less intense, and if it is associated with some apparent micturitional disorder, also in the presence of OSAS, it would be convenient to suspect or even to exclude concomitant pathologies of the lower urinary tract. The fact that 25% of the patients examined had a clinically significant urological pathology, without ever having been subjected to a urological examination, shows once again how often urological patients suffering from obstructive disorders return to the specialist too late. In fact, micturitional disorders often present very slowly and in different ways from patient to patient, and for this reason the patient only recognizes them when they threaten his everyday life in a significant way, or when they cause complications such as fever, urinary infection, or acute urinary retention. It is also important for the urologist to consider nocturia, not only as the effect of a possible urological pathology, but also as a possible symptom of other diseases such as OSAS and the common snoring; as suggested by the study when nocturia is intensive and associated with poor diurnal urinary symptomatology.

Nocturia is always a symptom which recognizes several causes, above all in the absence of other important symptoms; therefore, correct clinical evaluation is not easy.

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# EARLY PRESBYCUSIS IN OBSTRUCTIVE SLEEP APNEA SYNDROME

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## Introduction

Presbycusis is linked to the physiological deterioration of hearing due to age. In most cases, it is difficult to trace the borders between this physiological phenomenon and any pathological decrease in hearing, especially that due to unfavorable environmental factors, since the age of onset and the evolution of this clinical entity vary considerably.

Presbycusis is manifested audiologically by a symmetrical sensorineural high frequency hearing loss, which, as the patient gets older, spreads towards the middle and low frequencies.

Many etiopathogenetic hypotheses have been put forward, and in fact presbycusis is thought to arise from the amalgamation of many causes that may accelerate cochlear and retrocochlear aging, such as: dysmetabolism, hyperlipidemia, blood hypertension and atherosclerosis, and chronic acoustic trauma. In particular, atherosclerotic degeneration of the internal cochlear artery may reduce the blood supply to the labyrinth, thereby causing atrophic changes to, and the death of, the cells of the vascular stria.

Patients affected by obstructive sleep apnea syndrome (OSAS) experience prolonged and repeated periods of hypoxemia-hypercapnia during the episodes of apnea, and undergo chronic acoustic trauma as a result of the snoring noise. Since they usually also present with chronic blood hypertension, it is possible to suppose that they have a higher incidence of 'presbycusis type' sensorineural hearing loss compared to the general population.

The present paper will evaluate a wide sample of patients affected by OSAS with regard to the correlation existing between hearing loss, gravity of OSAS, and intensity of the snoring noise.

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## Material and methods

In order to characterize the OSAS hearing loss profile, all patients ($n$ = 63; 51 males, 12 females; aged 31-72 years; mean age: 50 years) underwent pure tone audiometry (PTA), impedance audiometry (IA) with the Metz test, and transiently evoked otoacoustic emissions (TEOAEs). TEAOEs were obtained with ILO88, registering their intensity, reproducibility, and power spectrum. OSAS was diagnosed by means of a two-night polysomnographic registration.

All 168 OSAS candidates answered a multiple-choice questionnaire regarding tinnitus and any other related symptoms or causes of middle and internal ear pathology. In this way, 105 OSAS patients with a clear history of well-known ear diseases were excluded from the present study.

During the polysomnographic studies, the weighted mean of snoring intensity (Laeq.t or equivalent sound level in dBA units) during one hour of sleeping was also recorded by means of a phonometer (sensitive to temporal variations of acoustic pressure) placed close to the patient's auricle.

The present paper reports on the grade of presbycusic hearing loss found in OSAS patients and studies the correlation between the apnea/hypopnea index (AHI), Laeq.t, and hearing loss characteristics with the aim of discovering a link between the early presbycusis observed in OSAS patients and the gravity of this syndrome and snoring noise intensity.

## Results

Audiological tests performed on the 63 OSAS patients showed bilateral sensorineural hearing loss, limited to the frequency range 2-8 kHz, in all ears. From the polysomnographic studies, the patients showed a mean AHI of 29 (range, 10-72); mean snoring noise intensity was 54 dBA (range, 50–58.8 dBA). Mean hearing loss for the 2-8 kHz frequencies was 24.9 dB HL.

The patients were divided in four groups according to age:

- Group 1 30-39 years ( 9 patients)
- Group 2 40-49 years (20 patients)
- Group 3 50-59 years (17 patients)
- Group 4 60 years and over (17 patients)

Group 1 had a mean bilateral 2-8 kHz hearing loss of 16.7 dB HL, and none of the patients in this group complained of tinnitus. The Metz test was positive in 30% of cases. TEAOE power spectra showed poor content at 5 kHz. Mean AHI was 29.1 and mean Laeq.t 50.7 dBA (with peak values of 72 dBA).

Group 2 had a mean bilateral 2-8 kHz hearing loss of 18.01 dB HL, and 10% of the patients complained of tinnitus in one or both ears. The Metz test was positive in 60% of cases. TEAOE power spectra showed poor content at 4 and 5 kHz. Mean AHI was 35.4 and mean Laeq.t 52.7 dBA (with peak values of 78.8 dBA).

Group 3 had a mean bilateral 2-8 kHz hearing loss of 31.12 dB HL, and 25% of patients complained of tinnitus in one or both ears. The Metz test was positive in 80% of cases. TEAOE power spectra only showed content at 1 and 2 kHz. Mean AHI was 29.2 and mean Laeq.t 51.8 dBA (with peak values of 87.7 dBA).

Group 4 had a mean bilateral 2-8 kHz hearing loss of 33.77 dB HL, and 50% of patients complained of tinnitus in one or both ears. The Metz test was positive in all cases. TEAOEs were only present in 25% of cases and power spectra content could only be evaluated for 1 and 2 kHz. Mean AHI was 22.3 and mean Laeq.t 51.4 dBA (with peak values of 75.3 dBA).

## Discussion

Many authors have underlined the role of hypoxemia in determining early presbycusis. Sohmer and Freeman[1] showed the effect of hypoxemia in causing hearing loss in animals, although results obtained in animal models are difficult to apply to human pathology. In cats, mice, and goats, they demonstrated that a reduction of only 20 mmHg of blood oxygen (with unvaried pH, $pCO_2$ and blood pressure) produces an increase in auditory brainstem response (ABR) threshold of between 12.5 and 22 dB SPL.

With regard to cochlear damage due to hypoxemia, in chinchillas (ranging in age from prematurity to 19 years), Bohne *et al.*[2] showed changes in the inner and outer hair cells, loss of dendrites in the ganglion spiralis, and degeneration of stria vascularis. These changes increased with age and were similar to those found in humans.

In 64 neonates with no viral or familial factors, but with severe hypoxemia (successfully treated with extracorporeal oxygenation), Cheung and Robertson[3] found a high incidence of high frequency sensorineural hearing loss (9.4% of cases).

Prolonged exposure to intense noise has been verified to be an important risk factor for early sensorineural hearing loss. It is important to understand the difference in the effects of acute and chronic acoustic trauma, since only the latter, as underlined by Kellerhals[4], appears to be responsible for progressive hearing damage.

Kellerhals studied 76 cases of acute exposure to intense noise (58 cases of bilateral acoustic trauma, 17 unilateral) who had undergone PTA about 20 years after the traumatic event. The hearing threshold of this control PTA had not deteriorated compared to the PTA carried out straight after the traumatic exposure, in those cases in which no other contributing factors had occurred during the time elapsing.

Prolonged exposure to noise is a well-known causative factor in chronic progressive hearing loss, as many authors have demonstrated in a wide range of the heavy-working population. One of the most recent studies shows that, after 24 years of exposure to intense noise (up to 90 dBA), 127 workers developed a mean 1-2-3 kHz hearing loss of 61.5 dB HL.[5]

## Conclusions

The sensorineural hearing loss found in the present study of OSAS patients has clinical features similar to those recognized under the name 'presbycusis', *viz*: high frequency hearing loss, lowered stapedial reflex differential threshold, TEOAE alterations, tinnitus).[6] In OSAS patients, this kind of hearing loss has the unique differentiating feature of appearing prematurely compared to homologous groups of subjects taken from the normal population (Figs. 1-4).

We therefore believe that OSAS may cause the earlier and more marked progress of presbycusic hearing degeneration that involves cochlear function (as seen by TEAOE alterations) and the central auditory structures, as previously mentioned in other studies.[7]

The hearing deterioration in OSAS patients appears to be linked to both the hypoxic and hypercapnic states, due to the lowering of the hemoglobin saturation rate, which causes the repeated nocturnal episodes of apnea due, in turn, to the upper airway obstruction. The prolonged nightly exposure to autogenous snoring noise also appears to play an important role.

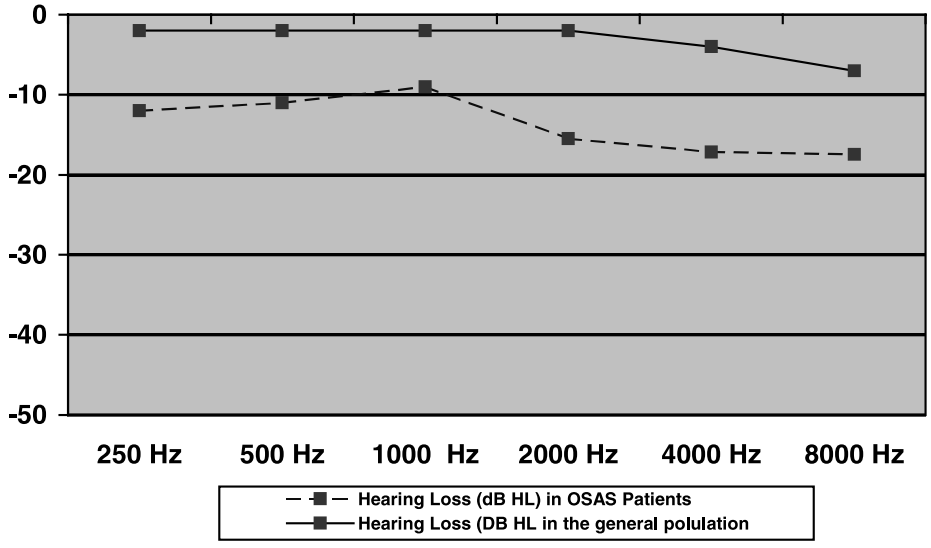


*Fig. 1.* Presbycusis in group 1 patients (30-39 years old).

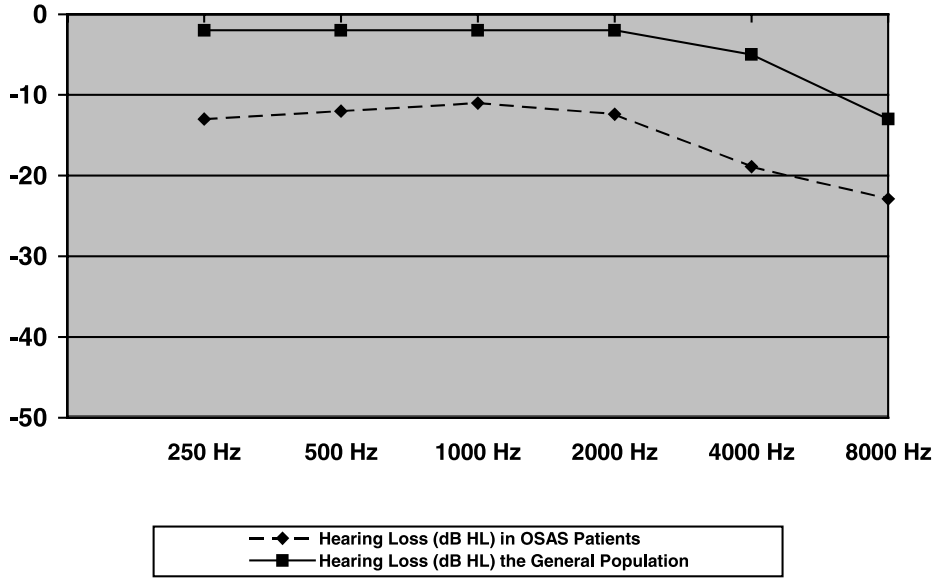


*Fig. 2.* Presbycusis in group 2 patients (40-49 years old).

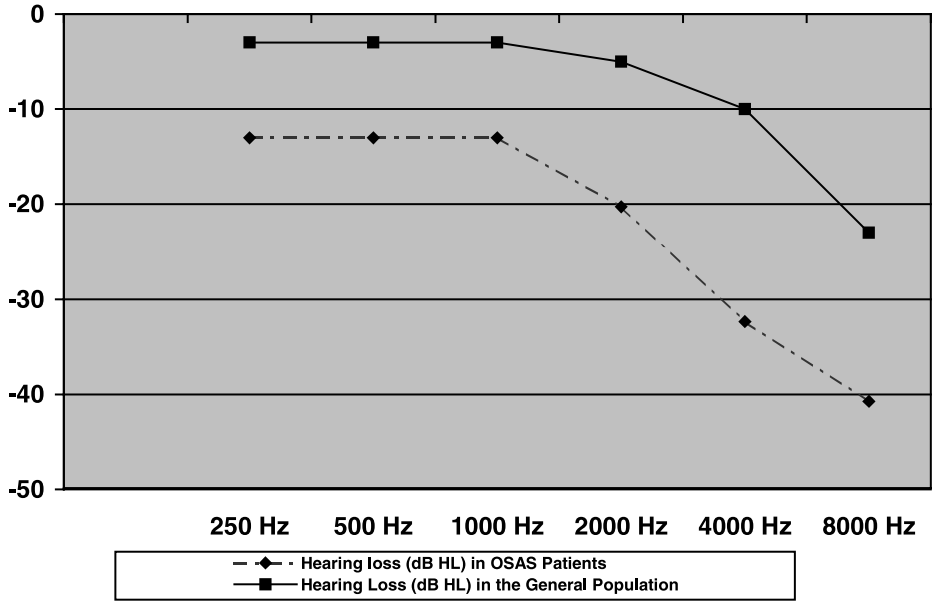


*Fig. 3.* Presbycusis in group 3 patients (50-59 years old).

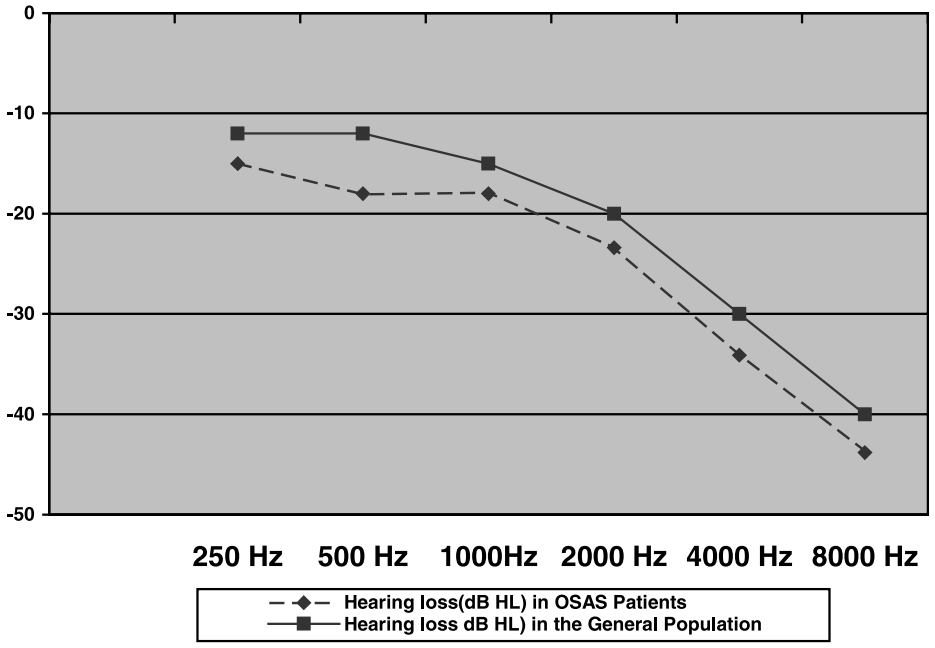


*Fig. 4.* Presbycusis in group 4 patients (>60 years old).

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# OBSTRUCTIVE SLEEP APNEA AND LUNG DISEASE

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Obstructive sleep apnea (OSA) and central sleep apnea (CSA) are matters of great interest. In subjects with this disease, both the etiopathogenesis and life expectancy decrease. There are, in fact, several causes of apnea (obesity, anatomical structure abnormality, alcohol, gastroesophageal reflux, alteration of the respiratory neural drive), but independent of this, it is important to emphasize that they can all induce hypoxia.

It seems likely that hypoxia is associated with a variety of hematological derangements, and cerebral and cardiac complications, such as pulmonary hypertension, cor pulmonale, and rhythm disturbances. The latter is often a cause of sudden death.

It is particularly important to devote attention to the association between respiratory alteration during sleep (OSA) and alveolar hypoventilation (Pickwickian syndrome) as well as that between chronic obstructive pulmonary disease (COPD) and OSA. In the last years, several studies have investigated the association between COPD and OSA, but this is still a subject of discussion. Certainly, patients with obstructive disease exhibit a greater likelihood of oxygen desaturation during sleep, because of the impaired ventilation-perfusion (V/Q) ratio, as well as a tendency for reduced ventilatory drive (respiratory neural central activity) and for obesity.[1] These patients are so-called blue bloaters (BBs).

BBs are swollen, edematous and cyanotic. In these patients, the increased respiratory activity, airflow obstruction, and impaired V/Q induce hypoxemia and hypercapnia. Prolonged hypoxia leads to an increase of erythropoietic synthesis and therefore to a further increase of erythropoiesis. It produces polyglobulia to compensate for the decreased oxygen to the tissues, thereby increasing cyanosis. Pulmonary vasoconstriction and blood viscosity increase,

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because of polyglobulia, causing pulmonary vascular resistance, overloading of the right ventricle, cor pulmonale, and the formation of edema.

BB patients are smokers and often suffer from recurrent bronchitis, coughing with mucous-purulent spitting, and dyspnea. They are incapable of increasing ventilation, due to more pronounced obstructions, more accentuated alterations of the respiratory pattern, and the respiratory center's decreased sensitivity to hypoxic and/or hypercapnic stimulus. It is not known whether the decreased sensitivity of these centers is influenced by acquired causes or by congenital alterations, as there is still a great deal of controversy regarding this subject.

BBs are characteristically obese subjects, and suffer from cardiac insufficiency, as well as decreased vital capacity (VC), increased residual volume (RV), normal total lung capacity (TLC), normal or decreased capacity for diffusion, decreased $PO_2$ and increased $PCO_2$, increased pulmonary arterial pressure (PAP), normal or slightly decreased cardiac output, and an increased total erythrocytic mass.

BBs exhibit central-acinar emphysema and impaired V/Q, while pink puffers (PPs) are characterized by pan-acinar emphysema and by a slightly impaired V/Q ratio, and furthermore do not suffer from significant hypoxemia and so are pinkish and thin.

PPs often breathe with half-closed lips in order to maintain a high endobronchiolitic pressure, so as to prevent the collapse of the lung parenchyma. PPs have dyspnea under stress, little cough and mucous spitting, and decreased VC, increased RV, normal or increased TLC, decreased capacity for diffusion, normal $PO_2$ and $PCO_2$, normal or increased PAP, decreased cardiac output, and a normal total erythrocytic mass.

BBs are characterized by greater diurnal hypoxemia than PPs. Therefore, the former probably also have more severe nocturnal hypoxemia.[1] Compared to patients with OSA only, BBs have greater hypoxemia.[1]

The mechanisms of hypoxemia in patients with COPD can be: hypoventilation,[2-4] defective respiratory mechanisms,[5-7] and impairment of gas exchange.[2,4,8,9] The term 'overlap syndrome' is used when COPD and OSA coexist in patients, but one author applied this term to indicate the association between OSA and pulmonary disease, such as in cystic fibrosis and pulmonary interstitial fibrosis.[8] The existence of the overlap syndrome OSA-COPD provokes two questions: does an obstructive disease signify a possible risk for OSA, and does the decrease of hypoxic drive predispose to OSA?[7,10] These two diseases are highly prevalent in the population, and common risk factors include cigarette smoking, excess weight, age and sex.[11-16]

The complications seen in OSA, resulting from nocturnal hypoxemia, are often the same as those seen in the overlap syndrome.[17] However, in the latter, more advanced pulmonary hypertension has been observed,[17,18] probably resulting from marked nocturnal hypoxemia and mild or moderate diurnal hypoxemia.

Many authors have hypothesized that OSA may accelerate the start of altered ventilation in patients with COPD,[17,18] while others believe that COPD may be the determining factor of complications during OSA.[19] In fact, hypox-

emia in patients with COPD leads to pulmonary vasoconstriction, the increase of pulmonary vascular resistance, and pulmonary hypertension, all of which may eventually lead to cor pulmonale.[17,18] In one study it was shown that, in the overlap syndrome, there may be a higher risk of developing respiratory insufficiency and pulmonary hypertension, although the degree of the obstruction in the patients examined was not very severe.[20,21] In fact, respiratory insufficiency and pulmonary hypertension are generally seen in patients with COPD and a severe degree of bronchial obstruction.[22,23] Therefore, in the overlap syndrome, the presence of pulmonary chronic disease or obesity would appear to be very important.

It is important to remember that, in patients with overlap syndrome, the level of pulmonary hypertension depends on the desaturation of oxyhemoglobin, and therefore it is important to establish the presence of pulmonary hemodynamic alterations and nocturnal hypoxemia. While some authors believe that pulmonary hypertension results from nocturnal desaturation, others believe that it basically depends on daytime arterial blood gases, rather than on diurnal hypoxemia and hypercapnia. This latter belief precludes mean nocturnal desaturation from being an independent value of PAP.[19,20,22] At the same time, these authors believe that the $PO_2$ and $PCO_2$ diurnal value can also be used as the pulmonary volume and predictive value of airway resistance, while they feel that the contribution of polysomnography is insignificant. They underline the relationship between hypoxemia-hypercapnia in OSA with bronchial obstruction and the dependence of a restrictive ventilatory pattern on obesity. Furthermore, they add that the number and duration of episodes of apnea do not play a determining role in the diurnal patterns of arterial blood gases. Therefore, it would seem to be important to investigate the possible presence of COPD in patients with OSA.[19,20,22] In patients with COPD, increased ventricular ectopia during sleep has also been demonstrated, and it worsened with desaturation of oxyhemoglobin of less than 80%.[24,25]

These data suggest that some patients with COPD die in the early morning hours, when more prolonged episodes of REM sleep occur (while there is severer degree of hypoxemia and a higher level of pulmonary hypertension).[18] Therefore, it is more likely that more profound hypoxyemias occur.

Several studies have evaluated the control of breathing in awake patients with OSA and in patients with overlap syndrome, and have shown that both groups have a higher neuromuscular output than control subjects. Patients with OSA probably have an increased output due to obesity leading to decreased thoracic compliance, but it may also result from increased hypoxic drive.[26,27] Other authors noted a decreased response during $CO_2$ stimulation in patients with overlap syndrome, while they observed a normal response in patients with OSA only. This is probably due to the presence of COPD and hypercapnic insufficiency.[28-30]

When comparing patients with COPD and normal subjects, increased neural drive has also been demonstrated during breathing. This increased respiratory drive is probably needed as an adaptive response to overcome increased airway

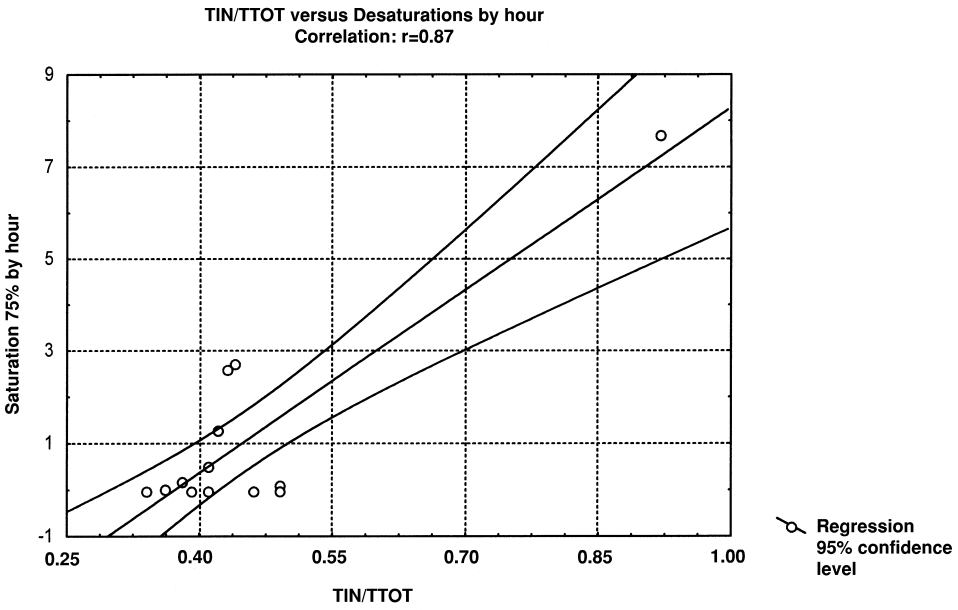


*Fig. 1.* Correlation between number of episodes of nocturnal apnea during each hour and the ratio TIN/TTOT in 13 patients with OSA.

resistance and decreased efficiency of the respiratory muscles.[28-30] It has been seen as a frequent association between OSA and Pickwickian syndrome.

Pickwickian syndrome is also defined 'obesity-hypoventilation syndrome': in these patients, their excessive weight may be a mechanical impediment to thoracic movements and obstructions can develop in the upper respiratory airways. In these subjects, the supine position particularly favors the development of hypoxemia. In Pickwickian patients, when there is OSA or CSA, hypoxemia or hypercapnia are more severe than in subjects with OSA or CSA alone. In these patients, a marked depression of hypercapnic or hypoxic drive has also been observed during the sleeping or awake states.[32,33] Furthermore, many authors have demonstrated inspiratory muscle weakness, increased respiratory drive and decreased tidal volume, compared with subjects with simple obesity.[31]

Patients characterized by the same degree of obesity (some eucapnic, others hypercapnic) were compared with awake patients with hypercapnia in order to correlate patterns of anomalous sleep and the control of breathing. Eucapnic patients demonstrated normal respiratory control which activated post-apnea hyperventilation, while hypercapnic patients demonstrated altered ventilatory control which did not allow for any compensation. It is not known whether the decreased drive in these patients is an acquired or hereditary abnormality.[34,35]

We examined a group of 13 patients with OSA (four females and nine males; mild or moderate body mass index (BMI; 29.31 ± 5.8); weight: 80 ± 18.2 kg;

age: 64 ± 4.5 years; height: 165 ± 8.3 cm), using spirographic patterns and the measurement of arterial blood gas at rest within standard limits. These patients underwent complete polysomnography with a 12-channel Respironix, which also included measurement of transcutaneous $PO_2$, to evaluate the number and the entity of nocturnal desaturations. The following day, the patients underwent spirography to determinate static and dynamic pulmonary volumes and measurement of arterial blood gas. We used a Jaeger ML3 spirometer.

We also evaluated the respiratory timing[36] of these patients, expressed by TIN/TTOT. TIN is inspiratory timing, while TTOT is total timing. We compared the number of important hypoxic events during each hour (saturation 75%). We observed a positive correlation ($r = 0.87$, $p = 0.000$) between TIN/TTOT and the number of hypoxic events (Fig. 1). Hence, the altered ratio TIN/TTOT resulting from the altered control of the respiratory center[36] is correlated to the number of nocturnal hypoxic events.

Our data suggest that the alterations in respiratory timing, the index of the respiratory center's neural control,[36] appear early in the natural history of these patients. In fact, the patients we examined had no alteration of respiratory functionality or alteration of arterial blood gas measurements.

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# SLEEP APNEA AND DRIVING

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## Introduction

It is estimated that 10-20% of all accidents are related to sleepiness. Among truck drivers and highway users, the figures are even higher. Lapses of vigilance cause more single-car accidents and casualties than any other non-drug related causes. Sleepiness may be caused by long working hours, sleep deprivation, shift work, alcohol consumption, as well as primary or secondary sleep disorders such as obstructive sleep apnea. Human circadian rhythm leads to very hazardous night driving, especially in young drivers.[1] Night driving performance has been estimated to be comparable to an 0.08% blood alcohol level while driving,[2] due to the hormonal and neurobiological pre-set-up for sleep.

Excessive daytime sleepiness and inattentiveness due to breathing-related sleep disturbances have in recent years been recognized as a major risk factor in traffic and industrial environments.[3] In severe cases, driving capability has, during simulated driving tests, been impaired to a level corresponding to controls driving with an 0.1% blood alcohol level.[4]

## Accident risk rates

Drivers suffering from obstructive sleep apnea syndrome (OSAS) are involved two to three times more often in car accidents than non-affected drivers.[5-8] Moreover, in highway accidents, OSAS drivers may be involved six times more often,[9] and in single-car accidents almost ten times.[7] The risk increases with the severity of the disease. Patients reporting frequent sleep spells at the wheel have the highest accident rates[7] and perform correspondingly poorly in simulated monotonous driving tests.[10]

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## Effect of treatment on driving and traffic safety

Both continuous positive airway pressure (CPAP)[11-14] and palatal surgery[15,16] have been shown to improve vigilance and driving performance, and to reduce traffic accident risk rates to normal levels. A substantial decrease of days in hospital after sleep-related accidents has been noted after treatment.[14]

## How to identify and deal with a hazardous driver

Unfortunately, it has not been possible to predict at-risk drivers from nocturnal sleep studies (nPSG), objective daytime tests of sleepiness (MSLT), the Epworth sleepiness scale, reaction time tests, or sleep questionnaires.[17] However, drivers reporting habitual sleep spells at the wheel and a frequent need to pull off the road for a rest are at high risk, especially if they have a history of near misses or accidents. This group of dangerous drivers, independent of apnea index, must be identified and given proper treatment. It is of great importance to create a confidential relationship with the patient. If they straight away fear loosing their driving license, they tend to deny or under report symptoms and mishaps.[18] However, the multitude of reports on successful treatment of non-vigilant sleep apnea drivers[11-16] provides hope of an optimistic attitude. It is of utmost importance to inform the driver of the known risks for him, as well as for his fellow road users. In addition, the liability for hazardous driving must be placed on the driver himself.

Examination and treatment should be given high priority, especially in the case of professional drivers. Temporary nasal CPAP treatment may be prescribed instantly, even to those who are on the waiting list for surgery. However, patients who are reluctant to utilize the prescribed therapy, or any clear-cut failures, must be reported to the authorities.

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# HIGHLIGHTS ON PATHOPHYSIOLOGY

# OBSTRUCTIVE SLEEP APNEA ASSOCIATED WITH RETROPHARYNGEAL LIPOMA

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Cervicofacial lipomas are relatively rare and only a few of them affect the retropharyngeal space.[1] Only about 20 cases have been reported in the literature,[2] and only two cases associated with obstructive sleep apnea syndrome (OSAS) have been described.[1,3] Retropharyngeal lipomas usually grow to a large size before they are discovered, and the initial symptoms are often related to the airways.[4,5]

We describe a case of retropharyngeal lipoma that caused OSAS. A 73-year-old woman whose body mass index (BMI) was 32 kg/m$^2$ presented to us because of the appearance of a stuffy nose, hyponasal voice, snoring, and a globus sensation. On further questioning, she was revealed to have severe daytime sleepiness as well. On rhinopharyngeal examination, it was noted that the patient had a soft submucosal mass pushing the posterior pharyngeal wall forward. CT scan showed a low attenuation bilobed retropharyngeal mass, measuring 5 x 2 x 2.5 cm, with sharply demarcated margins compatible with a lipoma, completely filling the nasopharynx and extending down to the hypopharynx (at the level of the C2-C3 passage). The preoperative evaluation also included flexible fiberoptic nasopharyngoscopy with the Müller maneuver, lateral cephalometric radiograph, and polysomnography. This last examination revealed severe OSAS (oxygen desaturation index (ODI): 43; mean $SaO_2$: 84%; lowest $SaO_2$: 60%; time of sleep with $SaO_2$ <90%: 35%). An attempt with nasal continuous positive airway pressure (nCPAP) treatment failed because of serious rhinopharyngeal obstruction. The severity of the sleep respiratory disturbance and the risk of potential postoperative airway compromise, led us to tracheotomy. The mass was removed transorally through a median incision in the soft palate and was confirmed to be a lipoma on histological examination. After surgery, all symptoms disappeared and postoperative polysomnography showed that the respiratory disturbance index was significantly reduced (ODI: 12; lowest $SaO_2$: 76%; mean $SaO_2$: 95%; time of sleep with $SaO_2$ <90%: 4%).

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This case shows that a serious obstruction of the rhinopharyngeal airway can be a prominent factor in OSAS. It can be seen from the literature that, after the mesopharynx, the next most common site of obstruction in patients with OSAS is the nasopharyngeal region. Obstructions at this site cause an increase in nasal resistance, which is followed by elevation of the inspiratory negative airway pressure in the pharynx. The aim of nasorhinopharyngeal surgery is to reduce nasal and/or rhinopharyngeal resistance, causing a reduction of negative pressure in the pharynx and eliminating oral breathing by shifting the position of the tongue and increasing the retrolingual space.

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# OBSTRUCTIVE SLEEP APNEA SYNDROME AND SOME NEUROLOGICAL DISORDERS

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## Introduction

Regulation of breathing during the different sleep phases is strictly controlled by the chemoreceptors of the carotid sinus and by the medullary respiratory centers.[1] In normal subjects, a typical decrease in respiratory rate may be accompanied by a variable number of asymptomatic apneic episodes (up to 40 per hour), each one lasting for less than ten seconds.[2] These brief interruptions of the respiratory cycle, more frequent during rapid eye movement (REM) periods, are considered to be a physiological phenomenon; they could be due to reduced brainstem sensibility to hypoxia in this sleep phase.[3] Central sleep apnea (CSA) can be defined as a more prolonged interruption of chest muscle function without any ventilatory effort.[4] CSA represents only a small percentage (from 10-20%) of all sleep apneas,[5] more often occurring in slim non-snoring subjects, and is probably caused by the temporary interruption of neural stimulation of the chest muscles. A vague borderline separates brief episodes of physiological apnea from true CSA.

Obstructive sleep apnea (OSA), provoked by temporary collapse of the pharyngeal lumen during the inspiratory phase of breathing, is by far the most common type of sleep apnea.[6] The sites of upper airway restriction are the nasopharynx and oropharynx because of the posterior displacement of the tongue base, and the horizontalization of the soft palate, a situation often coexisting with macroglossia.[7] In the majority of cases, people affected by OSA are middle-aged obese males, with marked hypertrophy of the pharyngeal walls and parapharyngeal connective tissue;[6] electromyographical studies carried out on these patients have revealed overactivity of the tensor palatini, inner pterygoid, sternohyoid, geniohyoid and, mainly, of the genioglossal muscle. This is probably due to the effort of keeping the pharyngeal lumen patent by pulling the tongue

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base anteriorly.[8] Synergistic activity of this group of muscles is markedly reduced during REM sleep, which could be an important cofactor in the ethiopathogenesis of OSA.[8]

## Aim of the study

Central and obstructive apneas seldom exist as separate entities, but more commonly a mixed pattern, in which both pathogeneses coexist, is observed.[9] Since central apneas have frequently been found to be associated with a major depression, and previous studies have shown a direct correlation between mood disturbances and tension type headaches,[10] the aim of the present study was to look for a possible relationship between apneic disorders and specific types of headache in a population affected by depression. The secondary goal of this study was to detect alterations in cytokines levels in subjects affected by sleep apnea, in order to verify any possible relationship between nocturnal awakening, tension type headache and immunological disorders.

## Patients and methods

In the period between January 1993 and January 1998, 754 patients were enrolled at the Headache Center of the Neurological Clinic, 'Federico II' University, Naples. All these subjects were diagnosed with migraine according to International Headache Society (IHS) guidelines.[11] Patients suffering from pure tension headaches (297 patients, 39.4%) were given a two-part questionnaire, the first part being the Rome Depression Inventory,[12] the second our own questionnaire mainly regarding quality of sleep, including snoring, dreaming and number of nocturnal awakenings. The questionnaires were catalogued on the basis of the patient's main complaint (nocturnal apnea, major depression). In order to detect any immunological alterations in people with sleep fragmentation, a group of 20 young male volunteers (mean age, 31.4 ± 4 years) was selected; ten of these subjects reported some degree of sleep disturbance, the remaining ten were completely normal. All the volunteers signed an informed consent form, in accordance with the Declaration of Helsinki. Selected patients underwent repetitive blood dosage of interleukin-1β (IL-1β) and β endorphin (β EPH) in the different sleep phases, by means of an antecubital intravenous catheter.

## Preliminary results

A retrospective study of the patients examined at our Headache Center revealed the coexistence of tension headache and some type of sleep apnea in 65 cases (8.6%), an association of depressed mood and sleep apnea in 118 patients (15.7%),

and the simultaneous presence of all these disorders in 25 subjects (3.3%). Blood specimens taken from volunteers with no sleep fragmentation showed a significant rise in IL-1β levels (mean increase, 8.7 pg/ml) during the night hours. Patients with sleep fragmentation, probably emphasized by the venous catheter, showed a significant increase in β EPH level during the night hours (mean increase, 15.7 pg/ml), together with a very low or undetectable level of IL-1β.

## Discussion

In a previous study,[13] our group noted the down-regulation of immune cells in patients complaining of repetitive nightly awakenings, frequently accompanied by intermittent snoring. While β EPH seems to rise in response to all kinds of external stress, it is unclear whether variations in IL-1β levels are a cause or a consequence of sleep fragmentation. It would be very interesting to find a clear cause-effect relationship between variations in IL-1β and β EPH levels and sleep fragmentation. Another unanswered question is whether the variation in IL-1β and β EPH is directly related to breathing disturbances, leading to sleep fragmentation.

Further studies are needed to confirm whether these immunological imbalances are provoked by tension headaches or depressed mood, or whether they are also present in normal subjects exposed to an occasional stress agent.

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# PEDIATRIC SNORING AND OBSTRUCTIVE SLEEP APNEA SYNDROME

# SLEEP-DISORDERED BREATHING IN CHILDREN

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## Abstract

Altered breathing during sleep is a common but poorly recognized finding in children. In the last 20 years, there has been increased interest amongst obstructive sleep apnea syndrome (OSAS) specialists in sleep-disordered breathing (SDB) affecting children. SDB comprises OSAS and upper airway resistance syndrome (UARS), an insidious form of nocturnal respiratory disorder that has significant clinical impact.

Over time, it has become clear that SDB behaves differently in children and adults, especially in relation to physiopathology, clinical scenario, and alterations in sleep. Thus, standardized diagnostic parameters, which are widely used to study adults, cannot be applied in children. Moreover, compared to adults, the true prevalence of clinical manifestations and complications in pediatric subjects is still under investigation. Although polysomnography (PSG) remains the gold standard investigation in the diagnosis of SDB in children, the clinical significance of established scoring criteria is still unclear. Alternative diagnostic means, perhaps useful as screening tools, have shown limited or insufficient specificity and/or sensitivity compared to PSG. Clinical judgement, with or without PSG comparison, should ultimately guide the therapeutic strategy.

Although PSG and adenotonsillectomy are considered by most specialists to be, respectively, the main diagnostic gold standard and management for SDB, currently there is no general agreement on which are the best methods of evaluation and treatment of SDB in children.

## Epidemiology

Obstructive sleep apnea syndrome (OSAS) in children was first described by Osler in 1892.[1] Since then, although numerous authors have focused their attention on adult OSAS – particularly during the last 30 years – relatively few studies have investigated the prevalence and nature of the syndrome in the pediatric population. The majority of these epidemiological studies has probably underestimated the true impact of OSAS, since they were conducted without a complete polysomnography (PSG),[2] and moreover, did not assess the

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presence of upper airway resistance syndrome (UARS). Nevertheless, according to the literature, the estimated prevalence of childhood OSAS ranges between 0.7% and 3%.[3,4] It seems that the syndrome is equally distributed between the sexes, and that African Americans are more frequently affected than whites.[3] The prevalence and sex distribution of UARS remains unknown, due to insufficient data.

## Pathophysiology

Sleep-disordered breathing (SDB) is a disease based on progressive disruption of the equilibrium between the intrapharyngeal pressure and pharyngeal dilator muscles. In normal subjects, the muscular action efficiently counteracts the intraluminal negative pressure generated in the pharynx by intrathoracic dynamics. Conversely, in SDB patients, several causes, either alone or in association, may alter the balance of intrapharyngeal forces. Anatomical, physiological and neurogenic factors, either alone or in combination, are responsible for the disorder.

There is evidence to show that SDB in adults is a continuum of the progressive stages of upper airway obstruction, from primary snoring (PS) to UARS, and ultimately OSAS.[5,6] These different manifestations of the same underlying process are caused by various degrees of upper airway (UA) narrowing, abnormal pharyngeal collapsibility, and neural regulation. Therefore, UARS is not currently viewed as a distinct pathological condition of OSAS. Although this is controversial,[7] it is possible that the same 'natural' progression observed in adult OSAS could characterize childhood SDB.

OSAS in children is defined as a nocturnal breathing disorder with prolonged partial UA obstruction and/or intermittent complete obstruction which alters normal ventilation and sleep architecture.

Following his first studies in children with increased nocturnal UA resistance,[8] in 1992 Guilleminault *et al*. introduced the term UARS to describe an entity with abnormal upper airway obstructions during sleep, in the absence of clear apneas and hypopneas and relevant oxygen desaturation.[9,10] UARS is characterized by increasing respiratory efforts, which can lead to hypopnea of one or two respiratory cycles and subsequently to arousal. These subtle respiratory changes can be assessed by monitoring esophageal pressure (Pes) through a nasopharyngeal catheter. Increasing values of negative Pes, in the absence of evident airflow limitations, terminate with arousal, and are termed respiratory-related arousals (RERA). RERA and spontaneous arousals from sleep are seen in children and should be scored in the evaluation of UARS.[11]

It still remains to be clarified whether or not PS has relevant clinical sequelae. The majority of studies comparing OSAS subjects diagnosed with PSG and those with PS, failed to show a clear difference between the two groups.[12-15] This interesting outcome, although an expression of the limited data, reveals

another important issue raised by Schechter,[16] and summarized by the American Academy of Pediatrics: "...with a poorly validated gold standard (PSG), statements regarding diagnostic accuracy of alternative methods of diagnosis become dubious".

Obesity is a very common feature in adult OSAS, but a relatively rare finding in the pediatric population where growth failure is reported more frequently. However, it is noticeable that obese children are at increased risk of developing OSAS.[17]

Adenotonsillar hypertrophy is universally considered to be the main pediatric cause in the pathogenesis of OSAS. Most OSAS children treated with adenotonsillectomy show clinical improvement. However, there is evidence to show that the size of the tonsils and adenoids is not predictive of the presence and severity of OSAS.[18] In other words, the degree of hypertrophy is not proportionally correlated with the severity of the syndrome. This finding suggests that other contributing elements should be considered in the assessment of children with OSAS, and in the evaluation of patients with persistent or recurrent symptoms and abnormal PSG parameters, despite adenotonsillectomy.

A discordant development of craniofacial structures may lead to abnormal UA respiratory functions. Both the maxilla and mandible play a crucial role in airflow dynamics since important muscles, such as the genioglossal and lateral pharyngeal wall musculature, originate at their surface. Thus, craniofacial dysmorphism can alter UA caliber, 'jeopardizing' the pharyngeal intraluminal equilibrium. Retrognathia, micrognathia, midfacial hypoplasia, high and narrow hard palate, Pierre Robin, Crouzon, Treacher Collins, and Apert syndromes have frequently been reported in association with disturbed oro-nasal respiration.[8,19,20] Deviated septa, enlarged turbinates, and hypertrophic or elongated uvula are also found clinically.[21]

Association of the clinical findings could increase the value of the clinical history in predicting OSAS. Guilleminault *et al*. studied 316 children (259 diagnosed with UARS and 83 with OSAS) and found that, when large tonsils were associated with clear craniofacial dysmorphism,[8] OSAS was more often present. However, the clinical scenario alone was not enough to distinguish UARS from OSAS. Similarly, many observers have shown that clinical disorders and evaluation cannot differentiate PS from OSAS.[13,22]

## Clinical scenario

Excessive daytime somnolence (EDS) and intermittent loud snoring characterize the typical clinical presentation of adult OSAS. In children, this association is rare, while habitual snoring and noisy or labored breathing are the common presenting symptoms. Interruption of breathing is more frequently seen in adults than in children, who often let out snores in association with brief movements (restlessness) during sleep.[2] Other clinical manifestations of the syndrome in

*Table 1.* Clinical features of OSAS in adults and children

| | *Adults* | *Children* |
|---|---|---|
| Snoring | intermittent | frequently continuous |
| EDS | frequent | rare |
| Obesity | frequent | rare |
| Failure to thrive | no | occasional |
| Daytime oral respiration | no | common |
| Sex (M:F) | <8-10:1 | 1:1 |
| Adenotonsillar hypertrophy | uncommon | very common |
| Obstructive pattern | obstructive apnea | obstructive hypoventilation |
| End apnea arousals | very common | uncommon |
| Sleep pattern | sleep fragmentation | normal sleep stages |
| Surgery | multilevel | mostly adenotonsillectomy |
| Continious positive airway pressure | commonly used | in selected cases |
| Complications related | cardiopulmonary/EDS deficit, perioperative, | neurocognitive, growth<br>cardiopulmonary |

Adapted from Carroll and Loughlin[41] by courtesy of the publisher

young patients include restless sleep, diaphoresis, enuresis and recurrent upper respiratory tract infections (Table 1).[2,23-25]

Growth deficit below the normal percentile range has been described in the literature as an expression of reduced caloric intake, secondary to tonsillar obstruction and elevated nocturnal energy expenditure, as a result of increased breathing efforts.[26] Recent studies, comparing pre- and postoperative results in children treated with adenotonsillectomy, suggest that OSAS may reduce the secretion of growth hormone (GH), which has physiological peaks during NREM slow wave sleep.[27,28]

Pediatric subjects may also present with a variety of behavioral and learning disorders, such as hyperactivity, aggressive attitude, and inattention.[2,3,12,13,29-36] According to the literature, "There is a nearly threefold increase in behavior and neurocognitive abnormalities in children with sleep-disordered breathing".[37] However, the majority of studies focusing on neurocognitive deficits related to SDB were conducted without control groups or objective sleep evaluation to distinguish PS from OSAS.[37] Therefore, in the light of the current pediatric literature, it is difficult objectively to assess the respective prevalence of behavior and learning abnormalities between PS and OSAS. As the latter is very unlikely in the absence of habitual snoring, the presence of snoring should warrant further investigation, starting with a detailed history of the child's sleep pattern and neurocognitive behavior.

Although infrequent findings, pulmonary[15] and systemic[15,38] hypertension and cor pulmonale have been reported in OSAS children with resolution following adenotonsillectomy.[37,39] Sudden infant death in association with OSAS has also been described.[40] The lack of accurate epidemiological studies pre-

vents the true prevalence of these complications in children from being established. However, it may be speculated that the increased awareness of OSAS in the pediatric population, followed by early intervention, has significantly reduced the number of such sequelae.

## Diagnosis

The study of children with suspected SDB has two goals: to verify the presence and frequency of nocturnal UA obstructive episodes, and thereafter to identify the site or sites of obstruction during sleep.

As stated above, no single symptom is pathognomonic for pediatric SDB and the clinical scenario cannot differentiate between habitual snoring and UARS and OSAS,[22] habitual snoring being a typical feature of both UARS and OSAS. The estimated incidence of habitual snoring is approximately four times greater than OSAS,[2,42,43] and therefore only a minority of habitually snoring children suffer from OSAS.

In order to evaluate the presence of abnormal respiratory and sleep parameters associated with UA obstruction, the clinical verdict should be supported by objective diagnostic techniques. The gold standard diagnostic evaluation for sleep disorders is polysomnography. As previously stated, "Childhood OSAS is not simply adult OSAS in little people and adult definitions and criteria are not applicable to children"[44]. Due to the large variability of cardiorespiratory parameters with age, the PSG scoring criteria used in adults have been modified in children, based on the following observations:

- compared to adults, apnea duration of more than ten seconds is much rarer in children, in whom shorter episodes of apnea can be followed by significant arterial oxygen desaturation;
- many children present with recurrent partial UA obstruction without total apnea;
- there is no direct relationship between obstructive events and oxygen desaturation;
- in many children, OSAS is not terminated by arousal.

Therefore, it is not feasible to apply data from studies performed in adult populations to children, since this leads to unacceptable underestimation of SDB.

Since Guilleminault *et al.* described the clinical manifestations of childhood OSAS as well as some of the relevant polysomnographic changes in detail,[45] more light has been shed on pediatric sleep medicine, specifically with regard to SDB. However, despite improvements in PSG scoring criteria in normal children,[46,47] the true influence of SDB on sleep remains poorly understood. Current PSG criteria for children older than one year follow the recommendations of Marcus *et al.*[46] and the American Thoracic Society.[47] Any obstructive apnea duration exceeding one apnea/hour is considered to be abnormal. Sus-

tained oxygen desaturation of less than 90-92% and/or greater than 4% from baseline is also considered abnormal. Since, in children, SDB manifests more frequently with incomplete obstructive events followed by reduced ventilation, *i.e.*, UARS, rather than with clear apneic episodes, it is recommended that a peak inspired $PCO_2$ ($P_{ET\ CO2}$) greater than 53 mmHg, or $P_{ET\ CO2}$ greater than 45 mmHg for more than 60% of total sleep time, should also be considered abnormal. However, Guilleminault *et al*., while acknowledging that until 1995 only very few studies had reported on UARS, pointed out that Pes, as an indirect measurement of intrathoracic pressure, is twice as sensitive as changes in $CO_2$ in identifying UARS.

With regard to the diagnostic dissimilarities suspected between adults and younger individuals, several studies have investigated pediatric PSG patterns and compared them with adults. Goh *et al*. found clear differences between previously reported adult PSG findings and their results in a pediatric population.[44] Above all, in accordance with other authors,[26,48,49] they noted how, in OSAS children, sleep architecture remains unchanged compared to normal controls and patients treated with surgery.[50] These same authors confirmed Guilleminault *et al*.'s observation that childhood OSAS is mainly an REM-related disease, and clearly showed how apnea index, apnea duration, and degree of oxygen desaturation were greater during REM than during NREM sleep.[45] Conversely, in adults, OSAS significantly alters sleep macrostructures by reducing sleep efficiency, slow wave and REM sleep.[51] Complete obstructive episodes are less frequent in children than in adults, and fewer cortical arousals occur in response to OSAS. In the absence of significant macrostructural abnormalities, the role of arousals from sleep has recently been investigated in OSAS patients. Arousals from sleep are an important defensive mechanism in UA obstruction. In adults, apneic episodes typically terminate with an arousal defined as an EEG frequency shift greater than three seconds.[52] These brief abrupt changes in EEG frequency, accompanied by neurovegetative activity, often determine a changeover to another more 'superficial' sleep stage that ultimately leads to fragmented sleep.[52,53] In children, partial obstruction is more frequent than explicit apneas which, however, tend to end without a detectable arousal. Moreover, in young patients, arousals are rarely followed by change in sleep stage.[50] Overall, the number of arousals from sleep in OSAS children is higher than in controls.[44] How this difference in arousal score is related to SDB symptomatology is still unclear. However, in order to 'justify' the clinical scenario of SDB, it could be argued that changes in sleep architecture may remain undetected with standard electroencephalographic techniques.[44] In summary, it is possible that alterations of the microstructure, rather than fragmentation of sleep stages, may be responsible for the neurocognitive deficits observed in OSAS children, whether cardiopulmonary sequelae are probably related to abnormal macrostructural patterns or to oxygen desaturation, as seen in adults.

Alternative diagnostic methods to PSG have been proposed over the years, most of which were critically analyzed by the American Academy of Pediatrics

in 2002. According to questionnaires in the literature, pulse-oximetry during sleep, nocturnal audiotaping and videotaping, nap polysomnography, ambulatory PSG and pulse transit time (PTT), should all be compared to PSG in order to be accurately evaluated. In this prospective study, more evidence is required on the validity of some of these additional diagnostic before they can be fully assessed.

Several questionnaires have been proposed in attempts to diagnose childhood OSAS. In 1984, Brouillette *et al*.[42] used a clinical OSAS score developed to assess three type of sleeping behavior: frequency of difficulty in breathing, propensity to snore, and observed episodes of cessation of breathing. They reported that the absence or high degree of OSAS could be identified by their scoring system. Inconclusive results were obtained with mild to moderate OSAS. Despite their initial promising report, which was, however, weakened by the lack of normal controls, ensuing studies investigating the accuracy of the OSAS score showed poor specificity and sensitivity, with more than one-third of cases being misdiagnosed.[13,22,54] Other questionnaires based on clinical history failed to prove predictive values compared to PSG.[55-57]

The measurement of arterial oxygen desaturation during sleep has been widely used as a marker of UA obstructive episodes. Pulse-oximetry is a useful diagnostic method, but only in patients who show clear evidence of desaturation. In fact, while the positive predictive value, compared to PSG, is extremely high, the negative predictive value is disappointingly low.[54,58] In other words, negative results harbor a large number of false negatives which require further evaluation with a formal sleep study. This is even more true if we consider how OSAS children frequently have short cyclic partial obstructive events, not followed by a drop in arterial oxygenation.

Daytime nap PSG has been evaluated in comparison with PSG. Such a study should last at least two hours and should include one phase of REM sleep. Again, similarly to pulse-oximetry limitations, nap PSG is a specific but not a sensitive method, and negative results must be confirmed by overnight PSG.[59]

Only a few publications have reported on nocturnal home videotaping and audiotaping as a screening tool in OSAS children. While specificity ranged from 71-94%, there was great variability between these studies with regard to specificity. This heterogeneity was probably due to different evaluation techniques and a lack of standard PSG criteria. Nevertheless, these techniques should be considered in support of PSG since their analysis may differentiate sleep and wakefulness and identify arousals more correctly.[60,61]

In recent years, PTT has been used to assess the presence of transient EEG arousals, and therefore sleep fragmentation. This technique was developed as an alternative method to PSG in the evaluation of SDB, and particularly of those respiratory-related events that occur without apnea, hypopnea, and desaturation.[62,63] PTT reflects the oscillations of blood pressure during the respiratory cycle, and is defined as the time delay between aortic valve opening during systolic pressure and the arrival of the pulse pressure wave at a peripheral site

(the finger). Thus, reduced PTT is an expression of the faster pulse wave propagation that follows a rise in blood pressure. Poyares *et al*. tested the accuracy of PTT for detecting arousals and sleep-related respiratory events (SRRE) such as apnea and abnormal breathing efforts.[64] They found a 90% sensitivity and a low specificity of PTT for recognizing both parameters. Individual variability, the occurrence of artifacts, and neurovegetative activities during REM sleep are limitations of this technique.[50,62] However, further studies are needed to better understand its clinical role in the diagnosis of SDB. Cephalometric analysis can be useful for recognizing UA patency in relation to maxillofacial structures.[65,66] Specific measurement criteria have been established to identify abnormal skeletal and soft tissue features. However, cephalometry shows a static and bidimensional image of anatomical structures with modest soft tissue resolution. Tridimensional imaging of pediatric UA with computed tomography (CT) and nuclear magnetic resonance (NMR) has also been studied, with differences being reported between OSAS patients and normal controls. Data obtained from imaging techniques may orient the therapeutical strategy, but should be analyzed within a complete clinical evaluation.

## Therapy

Adenotonsillectomy is the treatment of choice for the majority of children with OSAS. Improvement of symptoms and resolution of PSG abnormalities have been reported with a success rate ranging between 75 and 100%.[67-69] Several studies have shown the inadequacy of adenoidectomy as the only management treatment for OSAS. Most treatment protocols are empirically based or are influenced by anecdotal evidence rather than related to controlled studies. It is widely accepted that adenotonsillectomy is beneficial in the management of pediatric SDB, but only a few routine follow-ups have been reported that evaluate the postoperative recurrence of the pathology. Data are not available to verify the benefit of surgery on UARS patients. When adenotonsillectomy is not successful, patients should be offered mechanical ventilation support by continuous positive airway pressure (CPAP).[70,71] CPAP is often used in children who are overweight, or who show evidence of craniofacial dysmorphism, or in those with severe OSAS who are awaiting surgery. By keeping the pharyngeal lumen pervious, CPAP is a symptomatic but not curative treatment, and requires a long-term commitment. Compliance with this conservative but troublesome therapy is crucial, and is higher in older children.[70,72]

Ideally, children with SDB should have a maxillomandibular examination in order to assess the need for orthodontic treatment with repositioning devices to expand the oral cavity.[73,74]

Furthermore, in selected cases, newer treatment modalities, such as distraction osteogenesis of the mandible and midface, are valid options in the treatment of OSA during childhood.[75,76]

Tracheostomy is required in severe cases that do not respond to either conservative treatment or site-specific surgery.

## Conclusions

Although a common condition, SDB remains poorly recognized in children. Hypertrophy of the adenotonsillar tissue is responsible for the majority of cases of SDB. Snoring, noisy breathing, and restless sleep are typical presenting symptoms in these patients. However, clinical evaluation alone is unable accurately to discriminate between habitual snoring and UARS and OSAS, or reliably to predict the presence and degree of the obstructive episodes. Although pediatric polysomnographic parameters for both normal and OSAS children have been recommended, the clinical significance of scoring criteria is not yet fully understood. Currently, other techniques, such as nocturnal pulse oximetry, videotaping, audiotaping, and nap PSG still lack the necessary sensitivity to be considered an alternative to conventional PSG. PTT appears to be an interesting diagnostic method for assessing SDB, but further investigations are required to determine its clinical utility.

Early diagnosis is crucial for both treating and preventing the potential complications of OSAS. Adenotonsillectomy still remains the treatment of choice for SDB in children, but mechanical ventilation, orthodontic and maxillofacial treatments are useful options in selected cases.

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# OBSTRUCTIVE SLEEP APNEA SYNDROME

## An unknown pathology in children

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### Introduction

Obstructive sleep apnea syndrome (OSAS), first described in children by Guilleminault *et al.* in 1976, is a pathology characterized by repeated episodes of obstruction of the upper respiratory tract during sleep.[1] Obstructive apnea causes respiratory and cardiodynamic alterations, compromising the hypnoid function, with consequent daytime sleepiness and reduced performance during the hours of wakefulness.[2] OSAS in children is a complex pathology with a multifactorial etiology, habitually correlated to adenotonsillar hypertrophy, skeleton-facial anomalies and neuromuscular illnesses. Secondary risk factors are represented by: obesity, genetic syndromes (Down's, Pierre Robin's, Apert's, and Hurler's syndromes, etc.), craniofacial anomaly, laryngomalacia and some pathologies of the corpuscular components of the blood.[3-5].

In recent years, the diagnosis and therapy of nocturnal respiratory obstructions in children have been the subject of in-depth studies; in particular, the long-term effects of such a pathology on cardiac and pulmonary activities. It is, in fact, known that prolonged obstruction in adults can induce the onset of a cardiopulmonary syndrome mainly characterized by clinical signs such as systemic hypertension (50% of patients affected by OSAS), polycythemia, and cardiac arrhythmia.

The incidence of OSAS in children is still not well known; it generally begins at between two and five years of age (on average, 2.5 years in males and four years in females). In this age range the lymphoid pharyngeal tissue reaches its fullest development, with a prevalence in the pediatric population from six months to six years of age. Habitual snoring can be considered the preclinical phase of OSAS, involving 5-10% of pre-school children and approximately 27% of children older than six years.

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Respiratory disorders during sleep clearly characterize this pathology, with a 3% incidence in the pediatric population[6] and 19% in adults.[7]

## Physiopathology of the upper respiratory tract, central and peripheral apnea

The physiopathology of OSAS in pediatric patients and its multifactorial etiology are still not completely understood. The clinical manifestations appear when the relationship between the factors that maintain the respiratory tract and those that provoke its collapse are altered. The causes of OSAS are anatomical and functional in nature. The possible anatomical causes are those that induce a narrowing of the upper respiratory tract, determining an increase in the resistance to air flow. In children, particularly those aged between two and five years, narrowing of the respiratory lumen is a possible consequence of adenotonsillar hypertrophy. However, there is no direct proportionality between OSAS and the dimension of the lymphoid tissue. Nonetheless, during inhaling, movement itself is an important cause of the increase of resistance.

Craniofacial anomalies – hemifacial hypoplasty, micrognathia, syndrome forms, especially if associated with hypotonia or obesity – can contribute to determining reduction in the space of the upper respiratory tract, and consequently to determining the onset of OSAS. However, functional causes are associated with neurological diseases that reduce the normal muscle tone of the dilatator muscles of the pharynx, as occurs in Arnold Chiari's, Crouzon's, Marfan's, Prader-Willi's, and Hunter's syndromes. Typical snoring is directly related to occlusion of the upper respiratory tract caused by hypotonia of the pharyngeal muscles, or by the glossal muscles falling back. Therefore, the loss of muscle tone, physiological within certain limits during sleep, and morphostructural anomalies of the upper respiratory tract (macroglossia, adenotonsillar hypertrophy, craniofacial anomaly), when associated, become pathological.

Occlusion of the pharyngeal lumen can cause an arousal produced by activation of the reticular system, which is evoked by chemical and mechanical stimuli during apnea. Therefore, hypoxia, hypercapnia and pulmonary mechano-receptor stimuli play an important role in the return to normal ventilation. Apneas frequently cause fragmentation of sleep, which would explain both diurnal hypersomnia and modifications of the ventilatory function. In children, waking up during the night occurs less frequently than in adults, since children present a good sleep pattern. Alterations in the ventilator mechanism can induce oscillations in the pulmonary arterial pressure. In fact, the presence of hypoxic and hypercapnoid episodes cause vasoconstriction of the pulmonary arterioles, with consequent pulmonary hypertension and overloading of the right ventricle.

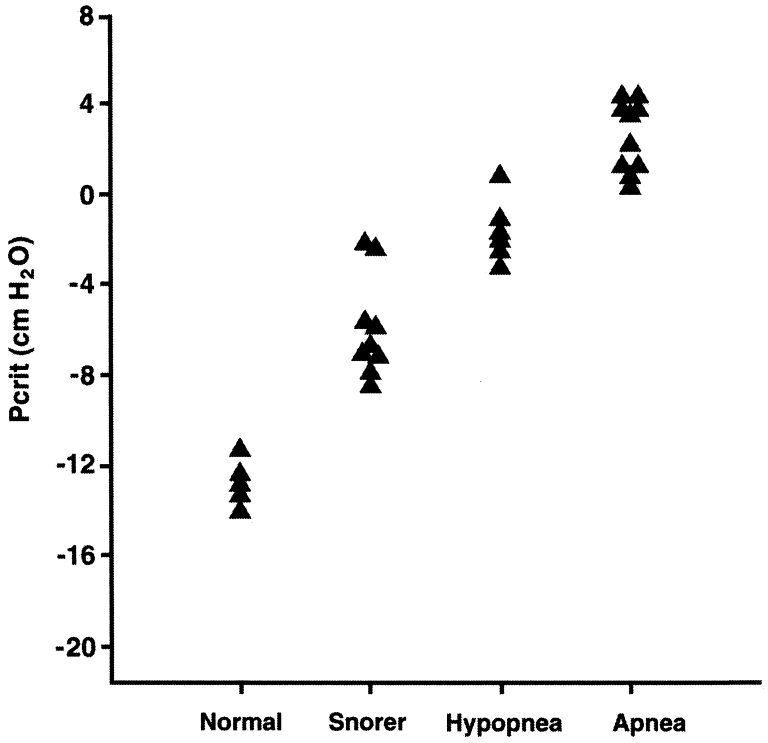


*Fig. 1.* The increase of Pcrit in children with snoring and apnea: relationship between Pcrit and occlusion of upper airway tract.

## Predisposing factors

In children, increase in resistance of the respiratory tract, caused in particular by adenotonsillar hypertrophy and nasal obstruction (allergic rhinitis, nasal septum deviation, choanal atresia) seems to be the major risk factor in OSAS, followed by syndrome forms and neuromuscular illnesses. Obesity alone is not enough to cause OSAS to develop, and is only an aggravating factor. During sleep, despite continuous respiratory 'effort', the superior airway locks, with consequent hypoxia and hypercapnia. If the obstruction continues, the activity of the accessory respiratory muscles increases, with a consequent increase in the negative intrathoracic pressure and complete occlusion of the upper airway tract, often accompanied by gasping (Fig. 1). Occlusion of the upper airway and hypercapnia are powerful stimuli for arousal, whereas hypoxia does not necessarily cause awakening. Arousal is habitually intended to be a transitory change in the stage of sleep, recorded by electroencephalography, until complete awakening.[8]

There can be up to 100 episodes of arousal during the night, thus causing fragmented sleep. However, this is characteristic of adults, while children awaken

less frequently and obstructions in their upper airways can continue for a long time without interrupting sleep.

Therefore, in adults, there is a reduction in the non-rapid eye movement (NREM) and rapid eye movement (REM) phases of sleep, with consequent diurnal hypersomnia; while in children with OSAS, the sleep pattern is preserved. In children, the apnea can be central, peripheral or of a mixed nature, due to an etiology that is often not clearly identifiable. Nevertheless, occlusion of the air passages, when present, if surgically corrected, would seem to improve the symptomatology of OSAS.[9]

*Adenotonsillar hypertrophy*

In children, secondary obstruction of the upper respiratory tract, due to hypertrophy of the adenoids and tonsils, is the principal cause of OSAS. Other underlying anomalies can also be present. In fact, the severity of OSAS is rarely proportional to the dimensions of the tonsils and adenoids, as has become clear from daily clinical experience: OSAS only develops among a few children with adenotonsillar hypertrophy. However, a child with slight lymphoid hypertrophy can be affected by severe OSAS.[10] Again, surgical treatment improves the clinical symptoms.

*Craniofacial anomalies*

Children with craniofacial anomalies often develop OSAS, especially in the presence of hemifacial hypoplasty, micrognathia, retrognathia or neuromuscular illnesses.

*Obesity*

Obesity is frequently associated with OSAS in adults, but much less often in children. In these patients, a delay in growth is more likely to be the cause of OSAS. In obese children, narrowing of the pharyngeal respiratory tract can be seen, due to the accumulation of fat both inside the muscles and in the soft tissue that delimits the pharyngeal region. Moreover, constrictive pulmonary illness (present in obese children) contributes to the appearance of night-time hypoxia; in these patients, the supine position is enough to cause hypoxia and, in addition, appears to be inadequate for the respiratory drive.

*The first month of life*

In the first month of life, children have predominantly nasal respiration and are prone to developing obstructions of the upper respiratory tract with increase in nasal resistance, as can be seen from the progress of a viral infection. In newborn children, there is ample soft tissue in the upper airway compared to its

bony part. The larynx is located in a cephalic position so that the epiglottis can rest on the soft palate, causing obstruction when the nose is closed. The jaw is more mobile and can be dislocated posteriorly, accompanied by the base of the tongue, especially when the baby is in a supine position. Nevertheless, position in itself would not seem to be an important aspect in the prevention of OSAS, while bending the neck can increase the collapsibility of the upper airway in children, perhaps determining a backward movement of the base of the tongue. In addition to these characteristics, the baby can also present with neuromuscular anomalies.

In fact, obstructions of the upper airway can be caused at a hypopharyngeal level, even in the absence of anatomical narrowing, and this has been attributed to lack of coordination of the pharyngeal muscles, due to immaturity of the nervous system. Certain thoracic characteristics are also important in pediatric patients who, in fact, have low residual functional pulmonary ability, so that small apneas can also induce desaturation. Another characteristic of OSAS in the first year of life is its strong association with the gastroesophageal reflux (GER). A recent study showed a strong association between GER disease and respiratory symptoms, such as apnea, cyanosis and stridor, in infants.

*Neuromuscular disorders*

Children with reduced neuromuscular tone, (*e.g.*, children with muscular dystrophia) are at risk for OSAS. Children with spastic neuropathy or muscular incoordination of the upper airway tract are also at risk for OSAS.

*Drugs*

OSAS can be caused or increased by the use of medicines – sedatives, anesthetics, etc. – that influence the activation of reticular formation, reducing the function of the respiratory drive or directly depressing the muscular tone of the upper airway. The hydrated chloral, also used for inducing sleep in polysomnography, depresses the tone of the genioglossus and, in isolated cases, is capable of causing OSAS.

*Hormonal effects*

In prepuberty, the incidence of OSAS would seem to be analogous in males and females, although male adults are more predisposed than females. The administration of testosterone can induce OSAS. This suggests that androgens play a role in OSAS, while estrogens would seem to have a protective effect.

## Clinical symptoms

In pediatric age, two symptoms are predominant: snoring and apnea during sleep. Snoring, particularly when noisy, is present during the night for a long time and is accompanied by an increase in thoracic-abdominal movements, followed by movements in the sleep. Frequently, the child awakens in a state of nervousness, with enuresis, profuse perspiration, and/or unusual sleep positions, such as on the elbows and knees, in an attempt to alleviate the respiratory difficulty.

Infections of the upper respiratory tract cause an increase in the gravity of the symptomatology mentioned above. The presence or absence of diurnal hypersomnia depends on the frequency and severity of the night-time symptoms, and therefore waking up in the morning is often difficult.

Excessive diurnal drowsiness is less common in children than in adults. Nevertheless, children can present with behavioral problems, such as difficulty in learning and low educational output, while hyperactivity sometimes alternates with excessive drowsiness and, finally, aggressiveness. Such symptomatology is often associated with a delay in physical development. This is partly attributed to anorexia or dysphagia, as a consequence of the adenotonsillar hypertrophy, or to increased respiratory stress during sleep, and partly to an anomalous secretion of the growth hormone released during the night, in relationship to the circadian rhythm.

Normally, the respiratory muscles use 1-2% of the basal consumption of oxygen, but in OSAS children, activation of the respiratory accessory muscles, in an attempt to guarantee ventilation, causes a sizable increase in the intake of energy, which affects growth. Children in whom the nasal obstruction is persistent are apt to breathe orally, and consequently have an adenoid facial expression.

### *ENT diagnosis in obstructive sleep apnea syndrome*

The diagnostic criteria include:
- accurate medical history of nocturnal and diurnal symptomatology;
- clinical observation;
- instrumental techniques (fiberoptic nasal endoscopy, imaging techniques (radiography, computed tomography, magnetic resonance imaging, and polysomnography).

It is also useful to consider various other conditions, as follows: weight, height, body mass index (BMI), and neck circumference. Some authors feel that such parameters should be considered risk factors.[11-15]

An accurate medical history can be built up with the help of parents, by compiling a special questionnaire. Clinical observation consists of careful evaluation of the physical characteristics, observing the child when he is breathing quietly.

A subsequent otorhinolaryngological evaluation can verify the presence of

nasal polyps, adenotonsillar hypertrophy, or hypertrophic rhinitis. Nevertheless, a detailed orthodontic assessment is also necessary. The presence of retrognathia or micrognathia, characteristic syndromes related to skull facial anomalies, or septal deviation, can lead to respiratory problems during sleep. Instrumental examinations can identify the macroscopic anatomical anomalies that can cause obstruction of the upper respiratory tract during sleep. These include radiography of the skull with visualization of the epipharynx, cephalometry, computed tomography, and pharyngolaryngoscopy. Such investigations only provide morphological information, without dynamically assessing the exact condition of the patient during sleep.[16-20] Therefore, polysomnography is still the principal tool for investigation. Examination of nasal respiration is important in children, since most inflammatory pathologies, adenoid hypertrophy and rhinosinusitis (aspecific and specific), can cause a nasal obstruction, and can therefore also lead to OSAS.

In the light of these observations, it is important that children with signs or symptoms of OSAS should be carefully examined by an otolaryngologist.

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# PEDIATRIC OBSTRUCTIVE SLEEP APNEA SYNDROME

## A multidisciplinary approach

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### Introduction

Obstructive sleep apnea (OSA) is one of the most common and serious sleep disorders to occur in children. Carroll *et al.*[1] reported that the incidence of OSA in children is between 1 and 3%, and that it affects children of all ages, from infants to teenagers. OSA is associated with many devastating neurological, cardiac, and developmental consequences, such as failure to thrive, cor pulmonale, and even death. Because of its potential for causing physical and psychological sequelae, being alert to the symptoms of OSA is imperative for pediatric and family practitioners, so they can refer patients for sleep evaluation. Numerous factors may predispose OSA to develop in children. Some of these factors are similar to those identified in adults, but several factors are different.

OSA is caused by certain mechanical and structural problems in the airway that cause the cessation or reduction of airflow.

Enlargement of the adenoids is normal in childhood. The reason why enlargement (hyperplasia) severe enough to cause obstruction develops in some children and not in others is unclear. Neither the thickness of the adenoids nor the actual size of the airway, determined on X-ray, is a strong predictor of obstruction. Although the most common time for enlargement to occur is at about the age of five years, symptoms of enlargement have been reported as early as at two months of age.

Several craniofacial syndromes are closely associated with snoring and apnea. The list includes achondroplasia, macroglossia, mandibular hypoplasia, Pierre Robin syndrome, Treacher-Collins syndrome, Crouzon's disease, Down syndrome, Prader-Willi syndrome, and Apert's syndrome.[2] Of these, mandibular hypoplasia is the anomaly most often implicated in OSA.

Some variation exists in the exact mechanism of obstruction from syndrome

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to syndrome, and airway obstruction may develop in patients with craniofacial malformation at any time, from childhood through to adulthood. The tonsils and adenoids are often the main cause of obstruction, or at least play some role in airway obstruction in these persons. OSA may occur in patients with neuromuscular disorders, especially those associated with muscular hypotonia and hypertonia. In these patients, a combination of abnormal pharyngeal muscle tone and hyperplasia of their tonsils and adenoids produces airway obstruction. Neuromuscular disorders that may be associated with OSA in children include, but are not limited to, the following: Duchenne's muscular dystrophy, myotonic dystrophy, nemaline myopathy, congenital muscular dystrophy, cerebral palsy, spinal muscular atrophy, transverse myelitis, and poliomyelitis. Obesity, which is commonly observed in adults with OSA, may also be a risk factor in children.[3] Although most children with OSA are not obese, anything that reduces the diameter of the nasopharyngeal airway (such as pharyngeal fat deposits) could predispose a child to the development of sleep-related upper airway obstruction.

The presence of allergy is frequently associated with an increased risk of OSA in children. McColley *et al*.[4] found that 36% of children who snored were sensitive to allergens, and that 57% of children who had OSA were also allergic. These figures compare with a level of allergy in the general pediatric population of approximately 12%.

Redline *et al*.[5] found that children whose parents or other relatives had a history of asthma are 3.5 times more likely to have sleep apnea than are children in unaffected families. This study of 235 children found that 11% of children in affected families had OSA, whereas only 3% of control subjects were affected.

Sinus problems contribute to airway obstruction by virtue of the narrowing that occurs as a response to exudate and inflammation. In addition, children with large, soft palates are more predisposed to obstruction because of the narrowing of the airway to accommodate the additional tissue.

Redline *et al*.[5] found that familial sleep-disordered breathing may partly be based on familial abnormality in the ventilatory control mechanism and possible anatomical airway narrowing. In addition, Mathur and Douglas[6] found that the sleep apnea-hypopnea syndrome has a strong familial component that may be caused by differences in facial structure.

If the adenoids and tonsils are large enough, they can obstruct any child's pharynx; however, several groups of children have a predisposition to pharyngeal obstruction with relatively small amounts of tissue. Children with craniofacial anomalies may have a smaller nasopharynx and oropharynx, and are likely to have obstruction.

In these children, normal or even minimal amounts of adenotonsillar tissue may cause severe obstruction. Children with Crouzon's disease, Apert's syndrome, Treacher-Collins syndrome, as well as unnamed minor craniofacial malformations, may develop pharyngeal obstruction shortly after birth, but usually

develop signs of obstruction as the pharyngeal lymphoid tissue enlarges. Patients with Down syndrome have some of the pharyngeal characteristics observed in craniofacial anomalies, and may have altered pharyngeal support. They also have a high incidence of pharyngeal obstruction.

Children with achondrophasia have similar anatomical characteristics that make obstruction common in this group.

Mandibular hypoplasia may also contribute to obstruction of the oropharynx by altering the shape and support of the oral cavity. Children with the Pierre Robin sequence have obstruction from collapse of the tongue into the pharynx and nasal obstruction when the tongue enters the cleft palate.

Adenotonsillar tissue in these children does not usually play a major role in the mechanism of the obstruction.

Patients with cleft palates, who have undergone a pharyngeal flap in order to correct velopharyngeal incompetence, may develop signs and symptoms of obstruction. The flap is designed to obstruct the lower portion of the nasopharynx sufficiently to reduce the incompetence. If the nasopharynx is occluded with adenoid tissue, or if large tonsils rotate into the pharynx, the combination of this tissue and the surgically created obstruction may be very significant.

Children with mucopolysaccharidosis (Hurler's and Hunter's syndromes) have a high incidence of pharyngeal obstruction. They may have a small pharynx, redundant tissue, altered airway support, and adenotonsillar hypertrophy, predisposing them to airway obstruction. These children may also have lower airway problems, making their management even more difficult.

Children with chronic inflammation of the nasal tissues, or deformities of the nasal cavity that are congenital or traumatic, may have an additional contributing factor. Severe nasal deviation is uncommon in children, but when it occurs, it may contribute to obstruction. Nasal congestion from allergic rhinitis or upper respiratory infections may cause intermittent acute signs of obstruction, whereas chronic inflammation may lead to polyp formation and cause signs and symptoms of chronic upper airway obstruction. This obstruction may vary in its severity, depending on the degree of inflammation and size of the polyps. Nasal polyps, chronic nasal congestion, chronic infections, and chronic nasal obstruction are also common in children with cystic fibrosis.

Children with altered neuromuscular tone may have poor support of the tongue and pharyngeal tissues. This, in conjunction with relatively small amounts of adenotonsillar tissue, may allow collapse of the tongue and the pharynx, leading to obstruction. Young children who have suffered anoxic central nervous system damage or who have congenital hypotonia ('the floppy baby') may have pharyngeal obstruction that may be intermittent and associated with central respiratory dysfunction that improves with growth and development.

Older children who have chronic neuromuscular developmental delay or progressive degenerative neuromuscular disorders often suffer from snoring and interrupted periods of breathing during sleep, which worsens as their muscular support deteriorates or as the adenotonsillar tissue enlarges.

Although the otolaryngologist evaluating a child must be aware of the predisposing conditions that contribute to obstruction and the unusual occurrence of space-occupying lesions in the pharynx, such as lymphoma and rhabdomyosarcoma, the vast majority of children with pharyngeal obstruction have adenotonsillar hypertrophy as the only cause, and otherwise appear to be healthy.

## Diagnosis

Polysomnography is still the most complete study for evaluating and characterizing chronic obstruction and sleep apnea in children.

Simultaneous recording of chest wall movement, nasal and oral airflow (thermistors), electrocardiography, electroencephalography, electrooculography, electromyography, and pulse oximetry may be performed in a sleep laboratory or hospital bed. Polysomnography is particularly helpful for differentiating central from obstructive and mixed apnea. Central apnea and apnea usually occur in neonates. Apnea related to gastroesophageal reflux can also be evaluated by adding an esophageal pH probe to the recorder.

Polysomnography is expensive, inconvenient, and does not lend itself as a practical screening device for older children with OSA or obstructive apnea. Moreover, there is less agreement on the criteria for diagnosis of obstructive apnea in children than in adults. In children, there may be more frequent episodes of partial obstruction and fewer episodes of complete obstruction than in adults.[7]

Hypoxemia and hypercarbia may also appear to be less severe. These limitations have led physicians to obtain polysomnographies in only the most severely affected children with adenotonsillar hypertrophy, in order to confirm what they have already established in other ways.

Multi-channel home-monitoring devices have the advantage of being less expensive, more convenient, and more likely to evaluate the child's natural sleep pattern, because they are used while the child is sleeping in his or her own bed. These monitors do not provide all the information available with polysomnography, but they are sufficient to assess patients with adenotonsillar hypertrophy and obstructive sleep problems.

Cutaneous oxygen and carbon dioxide monitoring in obstructive apnea patients is not as practical as the home-monitoring technique, but pulse oximetry has made the continuous monitoring of arterial oxygenation possible and convenient. This can easily be performed at home and provides a printed record of arterial oxygen saturation changes. Despite all the assessment techniques available, judgment as to whether adenotonsillar hypertrophy is present and whether the signs and symptoms caused by obstruction are significant, still rests on clinical judgment. The physician cannot rely on any standardized measurement provided in a laboratory to make the decision for him.

It has been shown that repeated episodes of severe obstruction can cause

asphyxial brain damage in infants. More frequent, but less severe, episodes may have a less dramatic impact, resulting in developmental delay. Judgment must be made as to whether the daytime performance of a child is correlated with the degree of obstruction and sleep disturbance. This becomes particularly important in older children when school performance is affected.

Failure to thrive and nutritional problems must also be taken into consideration.

Determination of the significance of adenotonsillar hypertrophy and obstruction must take into consideration the impact on the individual child and on the family. It is not reasonable to reassure parents that a child will outgrow the problem. Regression of adenoid and tonsillar tissue can occur in adolescence. The rate cannot be predicted in any individual child, and years of obstruction may take an irreversible toll.

## Treatment

The treatment of adenotonsillar hypertrophy as the sole cause of airway obstruction or in the presence of other contributing factors, such as craniofacial anomalies, is adenotonsillectomy. Relief of the obstruction is usually dramatic and improvement is noted immediately. When the obstruction is primarily caused by the adenoids, the tonsils should be removed as well. Tonsils that do not appear large may rotate into the pharynx, contributing to the obstruction.

The most common current method of managing children who are otherwise healthy, except for obstruction from adenotonsillar hypertrophy, is to perform their surgery on a same-day basis, if this is determined to be safe by the surgeon. Children under three years of age have a higher rate of respiratory complications and may require supplemental oxygen, artificial airway support (nasopharynx airway or endotracheal intubation), and management in an intensive care unit. Patients with severe apnea, craniofacial anomalies, and neuromuscular disorders can also have a difficult postoperative course, and are best managed as in-patients. For these children, it is wise to plan for hospitalization and to modify the requirement based on the child's recovery.

There are no fixed standard guidelines for the preoperative, operative, and postoperative management of a patient with adenotonsillar hypertrophy causing chronic airway obstruction, that are safe for all patients. These are judgments that should be made by the family, otolaryngologist, anesthesiologist, and pediatrician in order to maximize the safety of each child.

Nasal continuous positive air way pressure (nCPAP) therapy is a highly effective treatment for OSA, but there can be substantial problems with patient acceptance and long-term compliance. The most common surgical treatment for OSA is uvulopalatopharyngoplasty (UPPP), but this approach is limited by its variable success. Consequently, there is a need for alternative treatments for

OSA that are safe, effective, and acceptable. Oral appliances represent a relatively new approach in the management of OSA.

Schmidt-Nowara[8] have reported their experience with a mandibular repositioning appliance in 68 patients with either snoring or OSA. In 20 patients with follow-up polysomnography, this appliance reduced the apnea and hypopnea index (AHI) by more than 50% and improved both arterial oxygen saturation and sleep quality.

O'Sullivan *et al.*[9] recently showed that a mandibular advancement splint decreased AHI to < 20/hour in 12 of 17 patients in whom untreated AHI was 20-60 per hour, and in two of nine patients in whom untreated AHI was >60/hour. Eveloff *et al.*[10] reported their results with an anterior mandibular positioning appliance in 19 patients with OSA. Their success rate with this appliance was 53% when they defined treatment response as a reduction in AHI to < 10/hour.

There are major design differences in the numerous oral appliances that are now available and these may have an impact on their success and compliance rates. A novel oral appliance has been developed with an adjustable hinge that allows the progressive advancement of the mandible in order to achieve an optimal mandibular position. This anterior mandibular positioner (AMP) allows lateral movement, covers all the dentition, and provides good overnight retention. The object of this therapy, which we will call 'structural therapy', is the correction of dental malocclusion by means of special orthodontic appliances, of lips and tongue dysfunctions, and altered respiratory patterns by means of logopedistic treatments, and of muscle tensions and postural deviations by means of physiotherapy and chiropractic treatment.

It is very important to mention that not only can the orthodontist correct the open bite and mouth breathing, but he can also improve the dimension of nasal ways: in fact, by means of rapid separators applied to the middle palatine suture, it is possible to widen the nose base up to 10/12 mm. This correction of the ogival palate is associated with the reduction of bite distortion, or retrusion will enclose the intra-oral space, allowing the tongue to occupy a more advanced position.

In many cases, this is sufficient to restore nasal breathing and also to correct the developmental distortion of the nasal septum caused by the upward pressure of the tongue.

Resetting the mandible, when indicated, can be a solution to various muscle-tension headaches frames, relapsing otitis and dizziness.

Logopedists will try to correct atypical swallowing patterns, wrong attitudes of the perioral muscles, and to change the respiratory schema (less use of the thorax-clavicle structures, more of the diaphragmatic muscle). Physiotherapists and chiropractors will try to solve postural problems, detect possible concomitant negative postures, and modify the muscular schemes: for example, in case of a deep bite, it is necessary to obtain the mandibular elevator muscles or, in case of an open bite, to stretch the upper and lower hyoid muscles.

With this diagnostic and therapeutic approach, it is possible to detect and radically solve cases of respiratory pathologies where the pathogenetic role played by dental malocclusion is evident. If there is any doubt, it is still helpful to commence minimal orthodontic treatment, since this will not lead to any substantial contraindications or biologically damaging effects. If this treatment is not successful, it will be possible to find a surgical solution. When surgical treatment is absolutely necessary, contextual structural treatment is a good collateral therapy. In any case, it should be borne in mind that, if a malocclusion is present, sooner or later it will have to be treated. Therefore, orthodontic therapy should be considered as soon as possible, in anticipation of any therapy that will have to be performed later. For this reason, structural treatment of the obstructive respiratory pathology is not only highly satisfactory both for the patient and the doctor, but also it has no substantial biologically damaging effect.

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# HIGHLIGHTS ON PEDIATRIC OBSTRUCTIVE SLEEP APNEA SYNDROME

# PEDIATRIC SNORING AND OBSTRUCTIVE APNEA SYNDROME

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Chronic snoring in children ranges from simple snoring to obstructive sleep apnea syndrome (OSAS). Simple snoring is very frequent and, according to us, is seen in 3-27%, while obstructive sleep apnea is seen more rarely, in from 0.7-3%.

Breathing disturbances in children can cause worrying apnea during sleep, characterized by alterations in breathing and serious effects on the cardiocirculatory system (hypercapnia, pulmonary hypertension), which can cause sudden death.

It is very important to distinguish between simple snoring and sleep apnea, because the symptoms and causes are very different, and consequently treatment is also different. Correct anamnesis can help in the decision as to whether the child will need to undergo recording during sleep. Therefore, the careful examination of daytime and night-time symptoms is very important.

In simple snoring, daytime symptoms are very vague because the child does not experience somnolence during the day, since he is activated by toys and playing games. Night-time symptoms are characterized by intermittent snoring, often influenced by the position adopted during sleep. In OSAS, daytime symptoms consist of: hyperactivity of the child, a change in behavior, slight somnolence, headaches first thing in the morning, deterioration of intelligence with a low school output, and reduced development of height and weight. Night-time symptoms consist of snoring with shorter or longer phases of apnea, with breathing taking a considerable effort, troubled sleeping, sweating, enuresis, cardiac arrhythmia, and cervical hyperextension. During adeno-amygdaloid inflammation the patient suffers from rhinorrhea, audible day-time oral breathing, and pharyngeal dryness on awakening.

The etiopathogenesis of chronic snoring leads to obstruction in the upper airways. The accessibility of these airways is ensured by the pharyngeal dilatator muscles (genioglossus, geniohyoid, palatopharyngeal, stylopharyngeal, and tensor of velum palatinum). In the REM phases of sleep, the muscles relax, with consequent atonement, causing reduction of the size of the breathing space.

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This mechanism, which is physiological, in children as well, is emphasized by shrinking of the organs, caused by reduction of the airways. In children, there is a greater risk because the pharyngeal space is smaller, it depends on Landzert's angle, the larynges are higher, and the pharyngeal sweat tissue has greater lassitude, and moreover, adeno-amygdaloid inflammation is common at this age. If we add to this an inflammation or infection of Waldeyer's ring, the symptoms of obstruction become worse, including acute dyspnea with laryngeal croup even when awake, and cyanosis, serious enough to require sudden intubation.

In obstruction of the upper airways, adeno-amygdaloid hypertrophy makes up 65% of cases, genetic syndromes make up 30%, and in between we encounter Down syndrome, Pierre Robin syndrome (micrognathia with retrognathia, glossoptosis, and cleft palate), Goldenhar's syndrome causing facial malformation (hypoplastic jaw, stenotic nostrils, and small mouth), Treacher-Collins syndrome or mandibulo-facial dysostosis, Crouzon's disease (craniofacial dysostosis), bilateral choanal atresia, laryngeal palsy, laryngomalacia, congenital subglottic stenosis, laryngeal papillomatosis. Moreover, obesity accounts for 5% of cases (Pickwick syndrome). During adolescence, allergic or mucoviscidosic nasal polyposis and stenotic deviation of the septum are frequent causes of snoring.

Clinical diagnosis is based on a careful patient history which checks for day- and night-time symptoms, and on anatomical objectivity: adenoid facies, characterized by open mouth, short upper lip, separation of the superior incisors, ogival hard palate, retrognathia, and dental malocclusion. Oral breathing causes rhinolalia, there is reduced growth and weight gain, development of the chest is weak, leading to a concave sternum and sometimes to arterial hypertension. OSAS causes a change in behavior and character, the development of hypersomnia, asphyxia encephalopathy, arterial hypertension, and pulmonary heart disease.

Complementary diagnostic treatment consists of, firstly, a detailed otolaryngological examination, by means of video fibro-rhinopharyngolaryngoscopy with or without the Müller maneuver. X-ray examination is of limited use because the obstructive condition during sleep is a dynamic process and this examination must be performed when the patient is awake and in a static position.

X-ray examination of the skull in the lateral position can provide good visualization of the rhinopharyngeal space, because it is possible to measure the craniometric index and Landzert's angle, the length of the velum palatinum, the thickness of the base of the tongue, the distance between the joint of the mandible and the pharyngeal space. Obviously, computed tomography and magnetic resonance examinations provide more detailed information.

Polysomnography is the definitive test for demonstrating obstructive syndromes in children, because it documents any evident increase in respiratory distress (the effort to breath?), oxygen saturation, and increase in $CO_2$ during

REM sleep. It is necessary to check apnea/hypopnea indexes for several hours; 12 bouts of apnea occurring in a ten-minute time span over a period of several hours during noctural sleep is sufficient to make a definite diagnosis of OSAS. Oxygen partial tension is monitored continuously with an oximeter, any movement of the chest should also be monitored, and a continuous EEG should be performed.

It is not easy to carry out a polysomnography in a child: it is possible to make a digital recording of the oronasal flow, oxygen saturation, chest-abdominal movement, and cardiac frequency.

This series included 114 patients: 104 cases of simple snoring and ten of OSAS. Most of the cases of simple snoring involved adeno-amygdaloid hypertrophy. There were 93 normal children, nine children with Down syndrome, and just two cases of laryngeal papillomatosis. We only encountered ten cases of night-time apnea syndrome, two of whom had adeno-amygdaloid hypertrophy: one in a six-month-old child and the other in an eight-month-old child, transferred to us from a pediatric clinic for urgent adeno-amygdaloidectomy surgery. Three were affected by Down syndrome, three others by choanal bilateral stenosis, one by laryngeal subglottic stenosis, and one by subglottic hemangioma.

In conclusion, in our series, adeno-amygdaloid hypertrophy was present in 83.3%, genetic disease in 14.9%, and viral disease in 1.7%.

Medical therapy consists of local and systemic treatment with corticosteroids, receptor H1 inhibitors, and leucotriene receptor inhibitors. Initial therapy establishes the continuous positive airway pressure (CPAP) throughout the nose. This is a temporary treatment, which cannot be definitive. The best treatment is surgery, directed towards removing the causes of the obstructive disease. In children with simple snoring, the gold standard is well-executed adeno-amygdaloidectomy for dissection, with the simultaneous removal of any lymphatic hypertrophy of Waldeyer's ring. In OSAS, it is sometimes necessary to perform uvulopalatoplasty, with Hedge's bilateral resection of the palatopharyngeal muscles and partial resection of the uvula. In craniofacial malformations, it is important to perform plastic reconstructive cervico-facial surgery and sometimes temporary tracheotomy while awaiting definitive surgery.

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# NIGHT-TIME OBSTRUCTIVE APNEA SYNDROME IN PEDIATRIC PATIENTS

## Findings regarding growth

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### Introduction

Retarded growth is seen in children affected by obstructive apnea syndrome, which occurs very frequently with an incidence of from 27 to 56%. There are many suspected causes to explain this phenomenon. It is thought that the low caloric provision in these patients can be attributed to anorexia and secondary dysphagia, the latter being due to adenotonsilar hypertrophy. Moreover, elevated caloric consumption derived from an increase in night-time energy consumption during respiration could represent a further cause of imbalance between assumed and consumed calories.

Disorder in the phases of sleep typical of obstructive sleep apnea syndrome (OSAS) drastically reduces the number of REM phases, and consequently entirely alters the phases of sleep. Thus, the sleep significantly modified due to bad respiration is responsible for the anomalous secretion of some hypophysial hormones.

In 1996, Grumstein showed in adult patients that the secretion of growth hormone (GH) was lower before patients underwent ventilatory therapy with continuous positive airway pressure (CPAP). This therapy is able to restore well-structured sleep, thus increasing the slow wave phases and thereafter increasing hormone secretion.

### Growth hormone secretion

The secretion of GH is caused by somatotropic cells, which represent about 50% of the anterior hypophysis cells. The hypophysis contains from 3-5 GH/mg and produces 500-875 GH μg/day. GH is similar to human placental lacto-

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gen hormone, with a similar structure of 92%. The codifying genes for these two hormones are both located in chromosome 17. GH secretion takes place in a pulsatory way, serum levels are variable for most of the day, with four to eight secretion peaks after food consumption, physical exercise, during slow wave sleep (SWS), and sometimes without apparent cause. The half-life of GH in the plasma is 20-30 minutes.

GH is necessary for normal growth. Its lack causes deficient growth, its excess giantism; GH does not seem to act directly on growth, rather it indirectly stimulates the formation of other hormones. These factors are known as somatomedin or insular-similar factors (IGF-I), they are dependent on GH and seem to be accountable for the stimulus for growth.

Somatomedin C or IGF-I is the most important somatomedin for growth and is mainly produced in the liver, but also in other tissues in smaller amounts. It is a small basic protein (molecular weight: 7600) that circulates bound to a large vector protein (molecular weight: 140000). The complex has a half-life of three to 18 hours, while the free hormone has a half-life of 20-30 minutes. Consequently, IGF secretion remains relatively constant for 24 hours, in contrast to the fluctuations of GH. It is not known whether the liver is capable of integrating GH fluctuations with the production of somatomedin.

IGF-I is structurally similar to proinsulin and has similar insular actions. Moreover, GH is able to stimulate insulin secretion directly, helping it to reply to various stimuli. In fact, subjects with GH deficiency show a reduced insulin response to the administration of glucose.

In the prenatal and neonatal period, growth is independent of GH. Yet, IGF-I increases during pregnancy in relationship with the placental lactogen hormone, thus regulating the production of somatomedin. It is not certain whether somatomedin plays a physiological role in the uterus. IGF is present at birth, at about half the level of that in adult age, and this level gradually increases during infancy until it reaches adult values at between eight and ten years of age, significantly associated to the child's state of nutrition.

During the rapid growth period in puberty, elevated levels of IGF-I are present, even though there is no correlation of a linear type between these two parameters. In fact, it is thought that GH might even have a strong influence on growth.

Another important metabolic effect induced from GH is stimulation to incorporate amino acids in the proteins, this action being either directed or mediated by somatomedin; while some amino acids, *e.g.*, arginine, represent a powerful stimulus for its release.

Moreover, GH is characterized by two other important functions: it is an antagonist of insulin, with hypoglycemia representing a powerful stimulus for its secretion, while hyperglycemia inhibits it; and, it stimulates lipolysis.

Finally it is important to remember that secretion of GH is doubly regulated hypothalamically: its secretion is stimulated from the release of the releasing

hormone (GHRH), while it is inhibited by somatostatin or growth-hormone-release-inhibitory-hormone (GHRIH).

## Material and methods

### *Description of the group*

The study was conducted on a group of patients who presented for observation at the Division of Otolaryngology, Jesus Child Hospital, suffering from respiratory distress. The children had been evaluated during prepuberal age at between 24 months and ten years of age. They all presented with nocturnal respiratory disturbances and symptoms of OSAS. Of the 73 children studied, an obstructive apnea syndrome was diagnosed in 31, adenotonsillectomy was performed.

The diagnosis of OSAS was made after a careful case history had been taken, using a specific questionnaire for night-time respiratory troubles in pediatric age (Table 1); moreover, all the patients had been evaluated by objective examination and sleep monitoring. After adenotonsillectomy, they underwent domiciliary pulsoximetry examination.

*Table 1.* Questionnaire regarding respiratory disturbances during sleep in pediatric patients

| | *Yes* | *No* | *Sometimes* |
|---|---|---|---|
| Is the diurnal respiration of the child nasal? | | | |
| Is the diurnal respiration of the child oral? | | | |
| Is the night-time respiration noisy? | | | |
| Does the child present with apneas during the night? | | | |
| Is the sleep upset? | | | |
| Does the child wake up often? | | | |
| Does the child present with diurnal drowsiness? | | | |
| Are there any episodes of enuresis? | | | |
| Are there any deglutition difficulties? | | | |
| Has the child's voice been modified? | | | |
| Does the child have little appetite? | | | |
| Is there any growth retardation? | | | |
| Does the child have frequent changes of mood? | | | |
| Have you noticed any learning difficulties? | | | |
| Does the child complain of any episodes of cephalia? | | | |

Of these 31 patients, 21 were studied using polysomnography, the remaining ten with pulsoximetry monitoring. The choice of technique had no correlation with the severity of the clinical symptoms, but was dictated by the need to perform a more easily accepted examination in early childhood. Patients with chronic pathology, systemic, and skull and facial anomalies were excluded from the study. No sedation was used to induce sleep.

*Polysomnographic evaluation*

Evaluation of the patients was carried out one month before and two weeks after the surgical operation by means of 21 polysomnographic examinations, ten repeated pulsoximetric examinations for two nights preoperatively, and 31 pulsoximetric examinations at home in the postoperative period.

*Polysomnographic monitoring*

A polysomnographic device was used with the following channels:

- a saturation sensor, which registers variations in oxyhemoglobin saturation and may be able to associate apneic and/or hypoapneic episodes;
- a thermocouple for the oronasal flux, which calculates expiratory and inspiratory flux by the difference in temperature of the air;
- bands for thoracic and abdominal movements, which individualize the paradoxical movements of the chest and are associated with 'obstructive episodes' (fundamental in the distinction from 'central episodes' characterized by the absence of thoracic movements);
- electrocardiographic derivations used to verify possible alterations of rhythm; this is possible by identification of the 'R' wave of two 'QRS' complexes connected by the study of the 'R-R' interval;
- body position;
- a microphone placed at the jugulum, to identify and distinguish rhoncopathy from OSA;
- tibial band, only used to study patients affected by 'restless leg syndrome'.

Pulsoximetric examination was carried out in ten patients instead of a complete polysomnographic study. Saturation is registered every four seconds with the help of a saturation device with a memory. The respiratory parameters are prepared for analysis, by means of suitable software.

*Respiratory parameters*

According to the American Thoracic Society for the definition of apneic-hypoapneic episodes (Table 2), we surveyed the following parameters:

1. Oxygen desaturation index (ODI)
2. $SpO_2$ nadir
3. Percentage of time when $SpO_2 < 90\%$ defined as T90
4. Respiratory distress index (RDI)
5. Apnea index (AI)

*Table 2.* Hypopnea index for preoperative respiratory parameters

| *Patients* | *ODI* | *Nadir (%)* | *T90 (%)* | *AI* | *HI* | *RDI* |
|---|---|---|---|---|---|---|
| AV | 14 | 76 | 6 | 2 | 8 | 10 |
| CF | 1 | 74 | 4 | 0 | 9 | 9 |
| CP | 1.35 | 85 | 0.40 | 0 | 6 | 6 |
| CA | 4 | 83 | 0.30 | 1 | 7 | 8 |
| CD | 3.5 | 79 | 1.91 | | | |
| CG | 18.1 | 84 | 6.40 | | | |
| CC | 15 | 82 | 2 | | | |
| CA | 3.5 | 85 | 5.60 | | | |
| DL | 2 | 89 | 0.30 | | | |
| DD | 2 | 58 | 0.20 | 0 | 5 | 5 |
| DC | 19 | 73 | 0.60 | 1 | 2 | 3 |
| DM | 11 | 70 | 2 | 1 | 2 | 3 |
| FA | 2.3 | 76 | 3.60 | | | |
| FC | 40 | 50 | 29 | 0 | 9 | 9 |
| GG | 8 | 78 | 4 | 1 | 4 | 4 |
| GG | 32 | 73 | 4 | 0 | 4 | 4 |
| MS | 21 | 70 | 2 | 1 | 10 | 11 |
| MM | 2.5 | 85 | 2.05 | | | |
| ME | 137 | 83 | 1.40 | | | |
| MA | 2.1 | 89 | 1.30 | | | |
| NL | 24 | 68 | 3 | 1 | 37 | 38 |
| PF | 21 | 63 | 4 | 0 | 12 | 12 |
| PL | 48 | 52 | 14 | 2 | 11 | 13 |
| PR | 1.6 | 86 | 1 | | | |
| UI | 14 | 78 | 2 | 1 | 10 | 11 |
| RP | 3 | 88 | 0.30 | 0 | 6 | 6 |
| RG | 3.9 | 73 | 0.70 | 0 | 7 | 7 |
| SG | 22 | 52 | 6 | 0 | 6 | 6 |
| SA | 6 | 87 | 0.60 | 2 | 3 | 5 |
| TM | 7 | 85 | 0.50 | 1 | 5 | 6 |
| VL | 4 | 88 | 0.40 | 0 | 11 | 11 |

The missing data are from patients who only underwent night-time pulsoximetry

## *Growth and growth factors*

### *Findings*

The following parameters were analyzed in patients at the moment of hospitalization for the polysomnographic study:

- weight
- height
- body mass index (BMI)
- cranial circumference
- bony age

The final two parameters need a brief explanation. Measurement of the cranial

circumference has particular importance in infants to evaluate the variations in intracranial mass. In infants born at term, the cranial circumference is 34-35 cm, reaching 42.5 cm in females and 44 cm in males at six months. Subsequently, there is an increase of 2 cm in the second year of life and of 1 cm in the third and fourth years, with thereafter a slow and progressive increase up to 18 years of age, making a total of 5 cm.

Bony age is one of the fundamental parameters in the study of bony maturation after birth. In healthy children, the points of ossification, which radiologically represent calcification of the cartilaginous epiphyseal nuclei or of the tarsus or carpus bone, appear to be in accordance with a relatively constant chronology. The methods currently being used more frequently, particularly at the age of 18 months, include radiography of the hand and wrist, conventionally using the left side. Two methods exist, as follows:

1. Greulich and Pyle's method is the most well known and owes its popularity to its simplicity. An atlas of the radiographic reproduction of the hand and left wrist, corresponding to the mean of a particular chronological age, allows the maturity (based on the sex of the subject) of the carpus, metacarpus, and phalanges to be examined. In practice, the bony age of the subject is based on the chronological age of children of the same sex with the same degree of bony maturation.
2. Tanner and Whitehouse's method is more complex but is extremely exact. The authors describe eight stages for 20 bones of the hand and the wrist. Each of these corresponds to a score. The sum of the scores for all the bones represents the global evaluation of skeletal maturity, which can be converted into bony age when the latest score corresponds to the chronological age where the same score is included in the 50° percentile.

Interpretation of bony age must take into account the vast limitations of normality. As well as hormonal factors, numerous other factors can influence bony mineralization, such as heredity, race, caloric supply, proteins and vitamins. Delays can have various meanings, which are not easy to interpret, and these have to be correlated with stature and age on examination.

The parents of five patients withheld consent for X-rays of the hand for the evaluation of bony age.

*Hematic findings*

Two hematic samples were taken, the first one month before the surgical operation, including all routine preoperative check-ups as follows:

- total cholesterolemia and HDL cholesterol
- triglyceridemia
- total protidemia and albuminemia
- thyroid functionality with FT3, FT4, TSH
- somatomedin C or IGF-I, the latter determined as follows:

250 ml serum were added to 1 ml of 0.5 N hydrochloric acid solution so that

*Table 3.* Preoperative growth parameters

| *Patient* | *Weight (kg)* | *Height (cm)* | *BMI* | *CC* | *BA* | *BC* | *BA-BC* |
|---|---|---|---|---|---|---|---|
| AV | 15 | 10613.34 | 50.5 | 4.5 | 4.5 | 0 | |
| CF | 13 | 8816.78 | 49 | 1.5 | 3 | -1.5 | |
| CP | 24 | 10720.96 | 51.5 | | 4.5 | | |
| CA | 13.5 | 8816.78 | 50.2 | 1.5 | 2.5 | -1 | |
| CD | 15.5 | 97.7 | 15.94 | 52 | 3 | 3.5 | -0.5 |
| CG | 13.3 | 9016.04 | 51 | | 3 | | |
| CC | 24 | 121.5 | 16.39 | 51.5 | 6 | 6.5 | -0.5 |
| CA | 14.4 | 101.1 | 13.72 | 48.2 | | 3.5 | |
| DL | 17 | 11014.04 | 51 | 4.5 | 5.5 | -1 | |
| DD | 12 | 9413.58 | 48.7 | 3 | 4.5 | -1.5 | |
| DC | 21 | 10618.68 | 49 | 5 | 5 | 0 | |
| DM | 12.6 | 90.3 | 14.81 | 49.5 | 2.5 | 2.5 | 0 |
| FA | 19 | 12112.97 | 50 | 6 | 5.5 | 0.5 | |
| FC | 12 | 9513.8 | 49.5 | 2.5 | 3 | -0.5 | |
| GG | 14 | 9116.9 | 50 | 1.5 | 2.5 | -1 | |
| GG | 20 | 10518.14 | 52.2 | 4 | 4.5 | -0.5 | |
| MS | 10 | 8314.15 | 46.5 | 2 | 2 | 0 | |
| MM | 13 | 85.3 | 17.99 | 48 | 2 | 2 | 0 |
| ME | 12.5 | 8915.14 | 49 | | 2 | | |
| MA | 18.6 | 109.4 | 15.15 | 51.2 | 3.5 | 4.5 | -1 |
| NL | 16.5 | 11013.22 | 50.5 | 4 | 4.5 | -0.5 | |
| PF | 9.7 | 9210.63 | 45.6 | 1 | 2 | -1 | |
| PL | 53 | 149.7 | 24 | 53 | 10 | 10 | 0 |
| PR | 20 | 11614.86 | 51.2 | 5 | 5 | 0 | |
| UI | 13 | 94.8 | 14.71 | 48.5 | 3 | 3 | 0 |
| RP | 18.7 | 10516.32 | 51.2 | 3 | 5 | -2 | |
| RG | 14.8 | 101.3 | 13.72 | 53 | | 4 | |
| SG | 16.5 | 10315 | 49 | 2 | 3.5 | -1.5 | |
| SA | 14.26 | 12018.5 | 52.5 | 7 | 7.5 | -0.5 | |
| TM | 13.7 | 97.7 | 13.8 | 50.5 | 3 | 3 | 0 |
| VL | 16.2 | 109.5 | 13.46 | 51 | 5 | 5 | 0 |

the binding proteins removed the somatomedin for filtering. The extracted serum was marked by $^{125}I$ by means of rabbit polyclonal antibodies. The measurement of radioactivity was proportional to the quantity of IGF-I. The sensibility of the radioimmunological test (RIA: radio-immuno-assay) was approximately 20 μg/L.

Somatomedin measurement was repeated in the hematic sample as a postoperative check-up, 15 days after adenotonsilectomy.

*Postsurgical evaluation*

Thirty-one prepubertal patients, 13 females and 18 males, were studied (Tables 3 and 4). The mean age at the time of adenotonsillectomy was 6.1 years (range, from 24 months to ten years and two months). The mean time between

*Table 4.* Preoperative hematic parameters

| *Patients* | *C.TOT* | *HDL* | *P.TOT* | *TRIG* | *ALB* | *IGF* | *FT3* | *FT4* | *TSH* |
|---|---|---|---|---|---|---|---|---|---|
| AV | | | | | | 94 | 3.73 | 1.6 | 2.41 |
| CF | 192 | 38 | 7.4 | 91 | 4.5 | 155 | 3.26 | 1.09 | 0.96 |
| CP | 163 | 35 | 7.3 | 57 | 4.5 | 129 | 3.21 | 1.05 | 3.23 |
| CA | 151 | 49 | 6.8 | 39 | 4.1 | 127 | 3.83 | 1.1 | 4.03 |
| CD | 160 | 44 | 6.7 | 43 | 4.5 | 138 | 3.07 | 1.11 | 2.14 |
| CG | 150 | 35 | 7.1 | 50 | 3.9 | 152 | 4.21 | 1.86 | 1.64 |
| CC | 149 | 60 | 7.2 | 38 | 4.4 | 160 | 2.79 | 1.2 | 1.37 |
| CA | 150 | 56 | 7.7 | 39 | 4.2 | 54 | 3.33 | 1.49 | 0.6 |
| DL | 192 | 55 | 6.8 | 65 | 4.1 | 127 | 3.5 | 1.25 | 2.8 |
| DD | 159 | 44 | 7.1 | 61 | 4.3 | 45 | 3.19 | 1.1 | 1.16 |
| DC | 120 | 48 | 6.6 | 57 | 3.9 | 225 | | | |
| DM | 159 | 55 | 6.9 | 69 | 4.2 | 44 | 2.77 | 0.94 | 3.3 |
| FA | 113 | 62 | 7.4 | 23 | 4.5 | 137 | 3.35 | 1.24 | 3.5 |
| FC | 176 | 60 | 7.4 | 61 | 3.8 | 35 | 3.31 | 1.18 | 3.93 |
| GG | 155 | 52 | 7.2 | 52 | 4.2 | 58 | 1.96 | 1.05 | 0.57 |
| GG | 158 | 51 | 7.8 | 56 | 4.2 | 16 | 1.16 | 2.95 | 2.73 |
| MS | 169 | 38 | 7.0 | | 3.8 | 78 | 2.65 | 1.3 | 2.35 |
| MM | | | 6.4 | | 4 | 156 | 2.62 | 1.08 | 1.47 |
| ME | 182 | 45 | 7.5 | 75 | 4.2 | 76 | 4.6 | 1.56 | 8.22 |
| MA | 184 | 55 | 6.9 | 44 | 4.4 | 97 | 2.99 | 1.06 | 3.83 |
| NL | 159 | 61 | 7.1 | 52 | 3.9 | 132 | 3.04 | 1.15 | 3.4 |
| PF | 142 | 80 | 6.8 | 66 | 4.2 | 15 | 3.04 | 1.14 | 1.36 |
| PL | 168 | 44 | 7.0 | 67 | 4.2 | 289 | 1.51 | 1.09 | 1.35 |
| PR | | | 7.3 | | 4.4 | 44 | | | |
| UI | 135 | 48 | 6.7 | 48 | 4.2 | 96 | 2.74 | 1.09 | 1.35 |
| RP | 209 | 43 | 6.9 | 123 | 3.8 | 151 | 3.35 | 1.37 | 2.39 |
| RG | | | 7.1 | | 4.3 | 56 | 1.95 | 1.04 | 0.62 |
| SG | | | 7.7 | 83 | 4.7 | 18 | 4.07 | 1.07 | 6.56 |
| SA | | | 7.3 | | 4.1 | 97 | 3.52 | 1.1 | 2.29 |
| TM | 120 | 44 | 7.1 | 74 | 4.4 | 55 | | | |
| VL | 135 | 48 | 7.6 | 60 | 4.4 | 66 | 2.74 | 1.14 | 2.43 |

The missing data are due to insufficient hematic samples and priority was given to IGF-I, FT3, FT4, and TSH samples.

polysomnographic study and surgical operation was 23 ± 7.5 days, while that between pre- and postoperative studies was 46 ± 5.3 days.

The respiratory variables studied before the operation were obtained from the following values:

- mean ODI = 11.8 episodes/hour (range: 1-48 episodes/hour)
- mean AI = 0.6 episodes/hour (range: 0-2 episodes/hour)
- mean RDI = 9.2 episodes/hour (range: 3-38 episodes/hour)
- mean T90 = 3.53% of the recording time with $SpO_2$ <90% (range: 0.3-29)

After the surgical operation, the patients underwent oximetric evaluation and a second hematic sampling for IGF-I, the relative values of which are described in Table 5.

*Table 5.* Postoperative oximetric parameters and second IGF-I samples

| *Patients* | *ODI* | *Nadir* | *T90* | *IGF-I* |
|---|---|---|---|---|
| AV | 6.5 | 82% | 2.3% | 107 |
| CF | 1.0 | 88% | 1.3% | 101 |
| CP | 1.0 | 85% | 0.4% | |
| CA | 4.1 | 82% | 0.3% | |
| CD | 3.2 | 78% | 1.2% | 213 |
| CG | 12.0 | 84% | 3.4% | |
| CC | 5.2 | 86% | 1.3% | 220 |
| CA | 0.3 | 85% | 5.6% | 46 |
| DL | 1.7 | 89% | 0.3% | 261 |
| DD | 1.9 | 76% | 0.2% | 110 |
| DC | 12.1 | 86% | 0.6% | 285 |
| DM | 6.71 | 78% | 2.0% | 86 |
| FA | 1.2 | 86% | 1.6% | 204 |
| FC | 23.0 | 79% | 4.9% | 61 |
| GG | 4.0 | 83% | 1.3% | |
| GG | 3.8 | 79% | 2.2% | 53 |
| MS | 4.6 | 77% | 1.2% | 108 |
| MM | 2.3 | 85% | 1.0% | 201 |
| ME | 5.1 | 87% | 1.2% | 42 |
| MA | 11.0 | 89% | 0.3% | 137 |
| NL | 1.9 | 78% | 0.3% | 64 |
| PF | 13.7 | 87% | 3.3% | 48 |
| PL | 13.6 | 71% | 4.0% | |
| PR | 1.6 | 88% | 0.1% | 77 |
| UI | 6.7 | 81% | 0.4% | 123 |
| RP | 1.2 | 89% | 0.3% | 161 |
| RG | 1.7 | 84% | 0.5% | 112 |
| SG | 2.3 | 79% | 2.1% | 39 |
| SA | 2.1 | 87% | 0.6% | 109 |
| TM | 2.8 | 88% | 0.5% | |
| VL | 1.9 | 89% | 0.4% | 74 |

Consent for the second hematic sampling was withheld in six cases.

## Results

### *Respiratory parameters*

Since no polysomnographic check-ups were carried out after the surgical operation, the reference parameters that can be compared are from the ODI and the T90. Significant decreases in desaturation episodes per hour, *i.e.*, 42.7% (mean ODI postoperatively 5.04 episodes/hour), were observed. T90 was reduced to a mean value of 1.56%.

*Growth*

The parameters relating to body growth were not re-evaluated in the postsurgical period because a large study is now being carried out with a mean follow-up of at least a year.

*IGF serum levels*

The mean serum levels of somatomedin at the postoperative check-up were increased by about 12.7% compared to preoperative mean values. Such a value was calculated in the 25 patients who agreed to undergo the second sampling. Table 6 shows the values of each patient for both samples.

*Table 6.* Pre- and postoperative IGF serum values

| *Patients* | *Preoperative IGF-I* | *Postoperative IGF-I* |
|---|---|---|
| AV | 94 | 107 |
| CF | 155 | 101 |
| CP | 129 | |
| CA | 127 | |
| CD | 138 | 213 |
| CG | 152 | |
| CC | 160 | 220 |
| CA | 54 | 46 |
| DL | 127 | 261 |
| DD | 45 | 110 |
| DC | 225 | 285 |
| DM | 44 | 86 |
| FA | 137 | 204 |
| FC | 35 | 61 |
| GG | 58 | |
| GG | 16 | 53 |
| MS | 78 | 108 |
| MM | 156 | 201 |
| ME | 76 | 42 |
| MA | 97 | 137 |
| NL | 132 | 64 |
| PF | 15 | 48 |
| PL | 289 | |
| PR | 44 | 77 |
| UI | 96 | 123 |
| RP | 151 | 161 |
| RG | 56 | 112 |
| SG | 18 | 39 |
| SA | 97 | 109 |
| TM | 55 | |
| VL | 66 | 74 |

## Discussion

After surgery in children affected by OSAS, we have observed a significant increase of somatomedin C, the reason for which may be found in the various physiopathological conditions we described at the beginning of this article.

The physiological secretion of GH is cyclical and closely associated with the various phases of sleep. Quabbe *et al.* were the first to observe a correlation between GH secretion and sleep. Subsequently, other researchers added to these observations, suggesting a possible correlation between secretion of the hormone and SWS. On the other hand, Buzi *et al.* report that in prepubertal children, GH secretion is totally independent of the phases of sleep. In fact, we do not have any concrete evidence to show that the increase in SWS, which occurs following the resolution of OSA, is the direct cause of the increase in IGF-I.

In adult patients, an increase in GH levels has been observed after treatment with CPAP, associated with a significant increase in the global time of SWS. The reduction in the amount of SWS is capable of interrupting GH secretion, even if the exact correlation between them is not known. It can be assumed that SWS represents an indirect factor in the increase of GH secretion, rather than a direct stimulus for its secretion.

Similarly to what we have observed in adult patients, we are convinced that, even in pediatric age, the night-time respiratory disturbance associated with OSAS is correlated with the interruption of GH secretion. This would represent the principal cause of the retarded growth in these patients. Other conditions could be associated with such a factor, such as reduced night-time waste of energy, the disappearance of dysphagia, amelioration of the appetite, less recurrence of infectious episodes, etc.

It is thought that the higher caloric supply in these patients, once OSA has been solved, could stimulate GH secretion, acting as a feed-back system on the hypothalamus-hypophysial axis. However, in the present study, the second hematic sample for the measurement of IGF-I was taken 15 days after adenotonsillectomy, *i.e.*, after a period of semiliquid nutrition, and it was certainly not profuse. Therefore, we tend to think that this hypothesis, at least with regard to the results of our study, is the less reliable. On the other hand, we can hypothesize that the reduced fatigue seen in the respiratory muscles and the consequent minor waste of energy which patients experience during night-time respiration, once the obstruction has been resolved, can influence the caloric balance positively.

The small number of patients in the present study could be a relative limitation. However, we believe that the increase in IGF-I levels recorded by us is significant, and represents an important contribution to understanding the retarded growth in these children.

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# A NEW TECHNIQUE FOR THE DIAGNOSIS OF PEDIATRIC OBSTRUCTIVE SLEEP APNEA SYNDROME

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An insufficient measurement of respiratory effort during sleep can be associated with the false diagnosis of mild obstructive sleep apnea syndrome (OSAS) and upper airway resistance syndrome (UARS). OSAS is well covered in the literature, while little has been written about UARS. Patients with UARS were first described by Guilleminault *et al*. in 1993.[1] These patients showed excessive daytime sleepiness and presented with mild sleep disturbances of no identifiable cause with regard to breathing, following standard nocturnal polysonography. Nowadays, assessment of the severity and response to therapy of UARS and mild OSAS, particularly in children, relies on vague, subjective parameters. Strong suspicions of breathing disorders during sleep may be based on parents reporting symptoms such as snoring, oral breathing, slow growth, and recurrent infection. Comparison of UARS and OSAS in children indicates that there is a very great overlap of symptoms, which explains the discrepancy between clinical suspicions based on symptom analysis, and polysomnographic findings based on obstructive events only. Current evidence suggests that increased upper airway resistance only causes an increase in inspiratory effort. Therefore, monitoring increases in inspiratory effort has become an important part of sleep studies. The conventional technique for measuring inspiratory effort is via esophageal pressure (Pes), using either a balloon-tipped catheter or a catheter with a pressure transducer mounted on the end.

Esophageal pressure is the gold standard for the measurement of respiratory effort-related arousals, but other, less invasive, techniques are auspicious for assisting in the diagnosis of UARS or mild OSAS. Therefore, new validated and non-invasive alternatives to Pes measurement are needed to evaluate respiratory effort during sleep.

A particularly non-invasive alternative to Pes is pulse transit time (PTT). Normally, the heart pumps blood from the aortic valve to the periphery. Depending on elasticity of the blood vessels, blood volume, and contraction force, the wave pulse of the blood will take some time to reach the periphery (*e.g.*,

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the fingers). The time between the heart contraction (r-wave detected by electrocardiogram) and the arrival of the pulse wave at the finger (p-wave detected by an infrared pulse-oximeter probe) is the PTT.

Normally, during inspiration, the pressure in the thorax becomes negative compared to the atmospheric pressure; conversely, on expiration, there is a small positive pressure. When the upper airways become obstructed, the thoracic pressure swing must be increased in order to obtain a normal tidal volume. Estimation of the augmented thoracic pressure is a quantitative index for the work of breathing. PTT can reveal acute changes generated by high intrathoracic pressure swings encountered during upper-airway resistance in sleep.

In fact, this high thoracic pressure swing will result in a high PTT swing. In this way, measurement of the swing in PTT indirectly yields a quantitative measurement of the degree of upper-airway obstruction. Measurement of Pes remains the method of choice for demonstrating the repetitive gradual increase in negative intrathoracic pressures.

PTT may provide the simplest means for accurately assessing respiratory effort during sleep. It has some potential physiological limitations, which are less present in pediatric patients. In fact, it is influenced by fluctuations in autonomic tones and by the left ventricular condition induced by pathological conditions such as cardiac failure and drugs. Moreover, changes in the compliance of the arterial wall due to aging or atheroma are probably associated with a modified relationship between PTT and Pes values.

In conclusion, PTT is a potential non-invasive method for evaluating breathing disturbances during sleep, such as UARS, which needs closer examination in the future, especially in pediatric patients.

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# FACIAL AND DENTAL MALOCCLUSIONS IN ALLERGIC AND NONALLERGIC CHILDREN WITH UPPER AIRWAY OBSTRUCTION*

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Upper airway obstruction (UAO) due to adenoids and chronic rhinitis, with consequent mouth-breathing and snoring, is a frequent phenomenon during childhood, and can affect the normal development of the facial skeleton and cause dental occlusion. The most frequent causes of inflammatory UAO are infection or allergy.

In order to demonstrate whether there are any differences between dental and facial morphology in allergic and nonallergic children with UAO, the authors evaluated 86 snoring mouth-breathers (MBs) aged between five and 12 years, 50 of whom were allergic and suffering from chronic rhinitis, and 36 of whom were nonallergic with adenoid hypertrophy. All MBs were compared with 36 nonallergic children with physiological nasal breathing (nose-breathers, NBs) of the same age who displayed dental malocclusion. They all underwent anterior active rhinomanometry, as well as clinical and radiological cephalometric evaluations. The presence or absence of allergy was assessed by means of skin prick tests and specific serum IgE. All the results were compared statistically. Both groups of MBs showed similar pathological nasal resistance values, while the vasoconstrictor response was higher in allergic MBs. Compared to NBs, MBs more frequently displayed a deep palate, smaller SNA angle (which indicates the spatial position of the maxillary bone in the antero-posterior plane), higher FMA angle (which indicates the longitudinal growth of facial bones), and a greater tendency to crossbite and overbite. Allergic MBs had a greater tendency to develop crossbite, increased overbite, and a smaller SNA angle than nonallergic MBs; and, there was an even greater difference between allergic MBs and NBs.

The authors point out the importance of an advanced multi-sided approach in children who are MBs or snorers, in order to prevent the development of potential malocclusion. On the other hand, orthodontic treatment must always be preceded by a thorough allergological investigation as well as a clinical and cephalometric evaluation of rhinopharyngeal patency, in order to establish the causes of UAO and to restore nasal breathing, thereby ensuring the definitive correction of the malocclusion.

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# FACIAL PATTERNS OF CHILDREN WITH OBSTRUCTIVE SLEEP APNEA*

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*Introduction:* At the 1999 APSS meeting in Orlando, FL, the authors reported that adult obstructive sleep apnea patients had dolicho facial patterns.[1] They studied the facial patterns of children with obstructive sleep apnea.
*Subjects and methods:* The authors selected 29 children aged less than 15 years who still had their tonsils and/or adenoids, and who were suffering from sleep disorders (mean age of the patient group: 6.6 ± 3.1 years). They digitized lateral cephalograms using Ricketts' analysis and examined the facial patterns.[2] They then compared these results with the mean in a group of normal nine-year-old Japanese children (normal group, $n = 41$).
*Results:* Five children from the patient group (17.2%) still had tonsils, seven (24.1%) adenoids, and 17 (58.6%) had both tonsils and adenoids. There were significant differences ($p < 0.005$) between patient and normal groups regarding facial axis (patients: 81.8° ± 3.1; normals 86.0° ± 3.0), lower facial height (patients: 54.6° ± 5.3; normals: 49.0° ± 4.0), mandibular arch (patients: 21.2° ± 4.8; normals: 25.0° ± 4.0); total facial height (patients: 68.4° ± 4.5; normals: 64.0 ± 3.0), and MacNamara-Pogonion (patients: 9.1 ± 5.4 mm; normals: 6.0 ± 2.0 mm).
*Discussion:* Adult obstructive sleep apnea patients have dolicho facial patterns, and so do children, but data collected from children did not show a stronger tendency for dolicho facial patterns than those of adults. When the tonsils and/or adenoids obstruct the airway, strong negative pressure occurs in the chest. This negative pressure may cause retraction of the tongue and the mandible, so that the facial patterns of obstructive sleep apnea patients may become dolicho.
*Conclusion:* Children with obstructive sleep apnea had dolicho facial patterns.

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# DIAGNOSIS

# OBSTRUCTIVE SLEEP APNEA SYNDROME

## From the introduction of polysomnography to a multidisciplinary and multilevel approach

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### Introduction

Clear improvement in the understanding of obstructive sleep apnea (OSA) pathology began with the study of sleep phases and related pathologies. In this regard, polysomnography represented a fundamental step in relating sleep disorders to obstructive syndromes. This promoted the development of therapeutical strategies that required knowledge of sleep medicine, which started with an understanding of normal sleep. Since 1979 a variety of surgical techniques, together with medical treatment (continuous positive airway pressure (PAP)), have been popularized. The majority of these had limitations, deficiencies, complications, and compliance issues. In particular, success rates were usually disappointing in moderate to severe obstructive sleep apnea syndrome (OSAS).

This scenario led to the implementation of site-specific procedures in order to limit the possibility of unsuccessful and unnecessary surgery.

### Review of the literature

The first polysomnograms were performed in 1965 on patients suffering from 'Pickwickian syndrome', in which patients suffered from excessive daytime somnolence (EDS) and cardiorespiratory failure.[1-3] These studies led to the discovery of apnea and its effect on sleep, and proved the direct relation between respiratory sleep disorders and the syndrome. It became clear that many obese snorers who did not have cardiorespiratory failure suffered from sleep apnea and EDS, and that OSAS was much more common than Pickwickian

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syndrome. In severe cases, complete resolution of the obstructive episodes was achieved with tracheotomy.[4] Soon after, the clinical and physiopathological principles of OSAS were outlined. Since the 1970s, many data have shown that the majority of OSAS patients had been heavy snorers for years before developing the syndrome. Moreover, it was demonstrated that snoring was secondary to a narrowing of the upper airway.[5] Fujita *et al.*[6] introduced the first surgical technique, uvulopharyngoplasty (UPPP) which was aimed at addressing a specific obstructive site. Although UPPP is efficacious for snoring (76-90% success rate), with this technique less than 50% of OSAS patients showed a respiratory disturbance index (RDI) of less than 20 with a 50% reduction[7,8]

Laser-assisted pharyngoplasty (LAUP) was popularized by Kamami for the treatment of snoring, and can be performed under local anesthesia in a clinic setting.[9] This procedure needs to be repeated up to seven times and has less than acceptable results in moderate to severe OSAS patients.[8,10,11] Therefore, LAUP is indicated for simple snoring and mild OSAS (RDI <20, lowest oxygen saturation (LSAT) >85%) where the site of the obstruction is limited to the oropharynx. A new technique, uvulopalatal flap (UPF), introduced by Powell *et al.* in 1996, has similar indications. UPF is a modification of UPPP with the advantage of being a one-step conservative and reversible procedure, in case of velopharyngeal incompetence. It has similar success rates to UPPP.[12]

The disappointing surgical outcomes in OSAS stimulated a full evaluation of the mechanisms and sites of obstruction using endoscopic and imaging techniques.[13] It was shown that OSAS patients suffered from 'disproportionate anatomy',[14] consisting of a large base of the tongue, narrow mandibular arch, and mandibular deficiencies.[15,16] Others authors[17] determined that collapse of the lateral pharyngeal walls played a significant role in causing upper airway obstruction.

Based on this information, skeletal surgery was then considered a possibility for use in the correction of sleep apnea. In the early 1990s, Powell *et al.* developed the Riley-Powell-Stanford phased surgical protocol.[18] In this protocol, after a complete standard clinical evaluation, patients are divided into three groups according to the level of obstruction (retropalatal, retrolingual, retropalatal + retrolingual). During phase I each site/sites is/are treated by different techniques: UPPP for retropalatal obstruction; UPPP + genioglossus advancement (GGA) and hyoid myotomy (HM) for both retropalatal and retrolingual obstruction; and GGA/HM for retrolingual obstruction alone. Patients who fail phase I will proceed to phase II, which involves maxillomandibular advancement (MMA). The surgical cure rate was defined as continuous positive airway pressure (CPAP) with an RDI of less than 20 and a 50% reduction of the initial value. Phase II surgery was reported by the authors to be 90% successful at four to six months. Successful treatment of OSAS by MMA has been reported by many centers throughout the world (65% with RDI <10, 86% with RDI <20).[19]

This surgery is complicated, with a lengthy recovery time and a potential for

airway obstruction in the postoperative period. However, excellent results can be achieved in experienced hands.[20]

All OSAS patients should use nasal CPAP before considering surgery. The requirements for CPAP include strong patient motivation and intelligence. Unfortunately, according to objective internal computer metering, compliance for longer than four hours per night is less than 50%,[21] and is related to the severity of the disease. Innovations in PAP delivery (bi-level, demand PAP – DPAP) did not show better compliance than CPAP. Since non-compliant patients are exposed to the morbidity and mortality of OSAS, surgical alternatives are fundamental.

## Discussion

The 1960s were a fundamental decade for studying the physiology and disorders of sleep. The introduction of polysomnography gave a clear understanding of sleep phases and related pathologies. The growing interest in this new field soon highlighted the key role played by sleep disorders in the pathogenesis of obstructive syndromes.

Moreover, the increased awareness of the consequences of OSAS on cognitive functions, work performance and the cardiovascular system, stimulated the search for medical and surgical solutions, focused on correcting an insidious and complex disease rather than a simple and annoying symptom like snoring.

In this regard, the 1980s and early 1990s brought new knowledge, based on which different surgical techniques were developed and popularized. However, the improved understanding of OSAS physiopathology was only partially applied to clinical diagnostic criteria. This resulted in 'airtight compartment' surgery that helped to spread solutions often aimed at correcting a single obstructive site.

The last few years have seen a tendency to move in the opposite direction and, therefore, to choose surgical options that could address OSAS – usually moderate and severe cases – as a multilevel disease.

The improvement in and routine use of clinical investigations for OSAS have made a multidisciplinary approach essential for selecting surgical patients correctly. In fact, many studies have shown that an accurate overall knowledge of this sleep disorder should not be ignored in the process of defining topodiagnostic criteria. Therefore, it is important that otolaryngologists, pneumologists, neurologists and maxillofacial surgeons should contribute to guarantee a constant pre- and postoperative functional balance.

Rigorous selection criteria, based on standard radiological, endoscopic, polysomnographic and clinical evaluations, were first applied by the University of Stanford Sleep Disorder Clinic. The correct location of obstructive sites greatly improves diagnostic accuracy, enables the diffusion of a customized,

multilevel and less traumatic surgical approach, and therefore enhances therapeutical results.

Medical treatment also plays a role: dental appliances and in most cases CPAP, although poorly tolerated as a permanent option, represent possible alternatives to surgery.

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# POLYSOMNOGRAPHIC TECHNOLOGY

## Trends, education and certification

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### Abstract

The polysomnographic technologist performs a vital role in the diagnosis and treatment of sleep disorders. Already an integral part of clinical and research settings, some polysomnographic technologists have broadened their scope to include management and marketing of sleep centers, product support and sales, public and patient education regarding sleep hygiene and relaxation counseling, increasing public awareness about sleep disorders and working to shape public policy through advocacy. The field has shown significant growth due to obvious increased public awareness of sleep disorders worldwide. With this growth has come the need for accessible educational opportunities for technologists. Sleep technologists obtain certification through board examination to acquire the credential of registered polysomnographic technologist (RPSGT).

### Trends

Since the early 1970s, polysomnographic technologists have been the technical group specially trained to perform polysomnograms (PSG) for the diagnosis and treatment of sleep/arousal disorders, including the management of nasal positive airway pressure (nPAP) titration for obstructive sleep apnea syndrome (OSAS).[1] These individuals function independently to safely operate sophisticated medical equipment to record sleep/wake physiology.[2] They work under the direct supervision of a physician who practices sleep disorders medicine. The physician develops the protocols which technologists follow in performing PSG studies, including utilization of PSG for nPAP titration.

Technologists who perform PSG-related procedures must: be well-versed in instrumentation used in a sleep laboratory and have a command of the sleep-induced physiological changes in various body systems including, but not limited to, the neurological, musculoskeletal, cardiac, and respiratory systems;

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have a working knowledge of the physiological and behavioral alterations associated with sleep/wake pathology; be capable of interpretation of electroencephalographic, electrooculographic, electromyographic, electrocardiographic, and respiratory tracings so as to be able to intervene appropriately during a study. They are also familiar with the integration of PSG and nPAP equipment to titrate positive pressure against respiratory events and arousals; and have recognition of, and appropriate response to, critical events that can occur in sleep, such as cardiac arrhythmias, seizure disorders, and other medical emergencies. Physicians utilize the observations of technologists to assist in the identification of dysfunction in sleep/wake cycles, to diagnose breathing disorders during sleep, and to evaluate treatment of these disorders. The specific parameters selected for a given polysomnographic study (the 'montage') are determined by the nature of the patient's presenting complaints and the differential diagnosis.[1]

Polysomnographic technologists titrate nPAP for OSAS. This is an application of nPAP different from its traditional therapeutic use in intubated, ventilator-dependent patients.[1] In nPAP titration for OSAS, pressure is delivered noninvasively through the nose (or nose and mouth) to evaluate whether it can prevent collapse of the upper airway at the level of the palate, tonsils and tongue. The correct nPAP pressure eliminates pharyngeal collapse and arousals from sleep resulting from increased upper airway resistance. Determination of this optimal level of pressure is accomplished in the sleeping patient by titrating pressures against respiratory events and arousals from sleep.

The technologist's role in the sleep laboratory is not limited to the overnight sleep study. Many have sleep laboratory management experience. This scope involves hiring and supervising other technologists, performing outcomes and sleep laboratory quality assurance, assisting physicians in clinic operations, and devising appropriate marketing strategies. When the technologist has moved up to the highest ranking in the sleep laboratory, he or she will often make a career choice to accept new positions with equipment manufacturers and product support personnel or sale representatives. Companies hire these individuals due to their broad-knowledge base of products, having become familiar with concepts and products while in the sleep laboratory.

The technologist is directly involved in patient education concerning nPAP and sleep disorders, and takes this one step further when making an outreach to the public or community in sleep awareness events. In regard to marketing and public education, many American sleep laboratories have entered into partnerships with the National Sleep Foundation (NSF) in Washington, DC, for a program known as Community Sleep Awareness Partners (CSAP). Annual events surrounding National Sleep Awareness Week (NSAW) are highly publicized in the larger market media.

Nationwide activities in the USA during NSAW range from numerous media events to grassroots involvement, with sleep specialists, technologists, government leaders, corporations, volunteers and sleep laboratories and centers

working together to host special awareness activities and encourage Americans to make healthy, quality sleep a priority.[3] On March 28th, 2000, at the National Press Club in Washington, DC, the NSF was scheduled to release the results of its nationwide 'Sleep in America 2000' omnibus survey on Americans and sleep. Among other important statistics, this poll will highlight specifically how seriously fatigue affects our productivity at work, at school, and at home.

The collective habits and practices of everyday living that promote good sleep and optimal daytime functioning have been called sleep hygiene.[4] Although not practising counsellors or licensed psychologists, the polysomnographic technologist has ample opportunity during PSG hook-up time to remind patients of good sleep hygiene. Many times, reading material is suggested to patients by technologists to help them gain a better understanding of good habits at bedtime. Regarding insomniacs, technologists frequently describe the induction of the relaxation response by controlling mental activity and muscle tone. They suggest peaceful thoughts while telling the patient to consciously relax the muscles of the trunk, neck and limbs so that the reduction of the excitatory drive occurs.[5]

Regarding patient education, the technologist who spends time to introduce simple relaxation techniques to the patient prior to nPAP titration proves that it is an integral component of nPAP compliancy. The use of visual aids, especially those of upper airway physiology of the sleeping patient, are beneficial in creating the well-informed and hopefully more compliant nPAP patient during the study, and upon the patient's return home with nPAP.

## Education

In the USA, there is currently one technologist educational program that offers a stand-alone sleep program. Several electroneurodiagnostic schools offer sleep technology within their programs, and a few respiratory technician programs provide orientation into sleep technology as well. At this time, one program is known of in The Netherlands. In early 2000, the Association of Polysomnographic Technologists (APT) curriculum development committee was looking to develop curriculum guidelines for accredited educational programs for polysomnographic technologists and other projects that strengthen core competencies.[3]

## Certification/registry

The polysomnographic technologist is credentialed through a comprehensive registry examination. Candidates must complete a minimum of 18 months' experience in clinical or human research where duties performed are primarily polysomnography, or complete a minimum of 12 months' experience in clini-

cal or human research if proof of credentialling in a health-related field accepted by the Board of Registered Polysomnographic Technologists is provided (*e.g.*, nursing, respiratory therapy, etc). Applicants for the comprehensive registry examination must be currently certified in basic cardiac life support (BCLS), cardiopulmonary resuscitation (CPR), or its equivalent.[6]

## The total number of individuals working in polysomnographic technology is unknown

It would be beneficial to the field of polysomnographic technology to be able to accurately determine how many individuals perform polysomnograms worldwide. In some countries apart from the USA, medical residents and nurses sometimes work in the field and perform the role of polysomnography. The total number of individuals performing polysomnograms is unknown, as is the number of clinical and research laboratories worldwide. According to the executive summary of the 1999 APT demographics, salary and educational needs (DSEN) survey, 1680 APT members and 1300 laboratories served by one equipment manufacturer received surveys. APT membership as of February 25th, 2000 was 2006, and approximately 85% of the members reside in the USA, according to postal figures from the mailing of the APT's international quarterly publication. Additionally, respondents to the DSEN survey across all technologist job titles reported an average salary of $1508 for a two-week period, which is a 9% increase over the typical salary in 1996, and technologist laboratory supervisors by 13.4% for an average of $1774 for a two-week period.[7]

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# ESOPHAGEAL PRESSURE MEASUREMENTS

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## Introduction

Measurement of esophageal pressure swings by pressure transducers or balloons in the esophagus reflects the driving pressure across the upper airway. In this chapter, we will discuss clinical applications of esophageal pressure measurements in patients with sleep-related breathing disorders.

## Measurement technique

Pressure in the esophagus can be measured by means of pressure transducers or water-filled balloons mounted on a slim, flexible tube. After calibration and local anesthesia of one nostril, the tube is placed in the esophagus, in a similar way to a nasogastric tube. Sensors are usually placed in the lower third of the esophagus.

Chervin and Aldrich[1] investigated the effect on sleep architecture of esophageal pressure measurements by means of a water-filled catheter. The polysomnographic data obtained from 155 patients undergoing pressure measurements were compared to those of 155 matched control subjects studied by standard polysomnography. Although these authors detected some differences in sleep characteristics, the changes were small and not considered to be significant. Skadvedt *et al.* reported similar results.[2] In their study, 32 subjects underwent polysomnography with and without upper airway pressure measurements in randomized order. No significant differences were detected in the number or type of respiratory events.

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## Esophageal pressure measurements in the diagnosis of central sleep apnea

Obstructive sleep apnea is characterized by the progressive increase of respiratory effort during the course of the apnea. In contrast, central apneas are defined by the complete absence of respiratory effort during the event. Figure 1 illustrates the typical features of central apneas: absence of airflow, thoraco-abdominal movements and esophageal pressure swings during the apnea. During routine polysomnography, respiratory effort is usually measured by means of thoraco-abdominal strain gauges. However, the signal obtained only allows qualitative assessment of the respiratory effort. Inductance plethysmography allows semi-quantitative measurement of the respiratory effort, but its use is limited because proper calibration is required, and this is hard to maintain if there is any change in sleep posture during the registration period.[3] If sufficiently reliable, strain gauges could offer an alternative to inductance plethysmography in cases in which the quantitative measurement of respiratory excursions is not required.

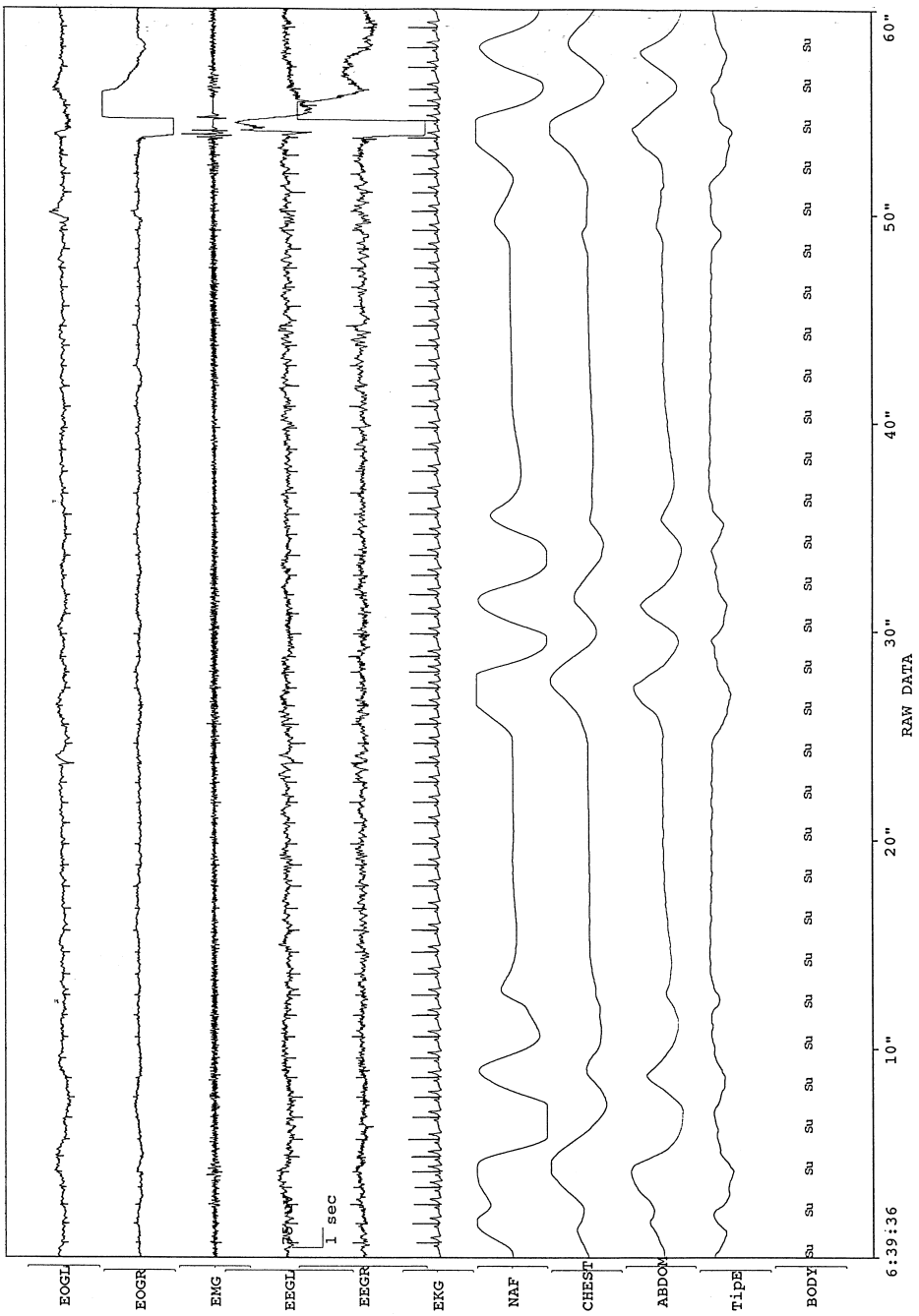
To investigate the agreement between results obtained by esophageal pressure measurements and by strain gauges, we analyzed the data of 22 patients in whom respiratory effort was measured simultaneously by means of an esophageal pressure transducer and strain gauges.[4] Detection of respiratory effort by strain gauges significantly overestimated the total number of central apneas in all the patients. Despite this overestimation, none of the patients was wrongly diagnosed as having pure central sleep apnea syndrome. Strain gauges are sufficiently reliable for the characterization of apneas in most patients. When strain gauges reveal that most apneas are central in origin, verification by esophageal pressure measurements is recommended.

## Esophageal pressure measurements and upper airway resistance syndrome

The measurement of esophageal pressure is instrumental in the diagnosis of 'upper airway resistance syndrome'. This condition was first described by Guilleminault *et al.*[5] as being the combination of a clinical complaint (daytime sleepiness) with the demonstration of flow limitation and increased respiratory effort with arousal from sleep, immediately following the peak negative inspiratory pressure. Peak inspiratory esophageal pressures of up to –10 $cmH_2O$ are considered normal during sleep.[6] Esophageal pressures that are more negative than –50 $cmH_2O$ can be observed in patients with obstructive sleep apnea syndrome, and also in patients with upper airway resistance syndrome.[7]

→

*Fig. 1.* Central apnea, defined by the complete absence of airflow, thoraco-abdominal movement, and esophageal pressure swings. From top to bottom: electro-oculogram (EOG), chin muscle electromyogram (EMG), electro-encephalogram (ECG), electrocardiogram (EKG), nasal airflow (NAF), thoracic strain gauge (CHEST), abdominal strain gauge (ABDOM), esophageal pressure (TipE), and body position (BODY).


EOGL
EOGR
EMG
EEGL
EEGR
EKG
NAF
CHEST
ABDOM
TipE
BODY
1 sec
6:39:36
10"
20"
30"
40"
50"
60"
RAW DATA

**Study of the mechanical response to upper airway occlusion**

Obstructive apnea is defined by the persistence of respiratory effort during periods of interrupted airflow. The increasing respiratory effort causes the development of negative intrapleural pressure, which is transmitted to the upper airway and esophagus. Berry *et al.* suggested that the maximum negative inspiratory pressure generated during upper airway obstruction is a measure of ventilatory drive and reflects the activation of the respiratory centers by chemical and mechanical input.[8]

The response pattern of the respiratory muscles to upper airway occlusion is likely to be affected by the duration of apnea, apnea-related hypoxemia, diaphragm fatigue, or the intensity of the respiratory drive response to obstruction.[9] For example, hypoxemia and muscle fatigue may enhance chemoreceptor and mechanoreceptor stimulation to the respiratory centers. This would, in turn, affect respiratory output (drive). Therefore, while the measurement of esophageal pressure may be used to evaluate central respiratory output during sleep, it should be borne in mind that the pattern observed is not solely determined by respiratory drive.

The initial decrease in esophageal pressure (Pes) swings during the first occluded breaths is followed by a progressive increase in respiratory muscle activity and Pes.[10] Maximum esophageal pressure is typically reached by the last or second last occluded breath. At the end of apnea, hypoxemia and hypercapnia are associated with a maximum increase in esophageal pressure and diaphragm activity. Both chemically- or mechanically-induced reflexes may induce the arousal response at the end of apnea.[11]

Three indices of respiratory effort can be described: overall increase in respiratory effort during obstructive apneas, rate of increase of respiratory effort and maximum respiratory effort at the termination of apnea. These indices can be used to evaluate the mechanical response to upper airway occlusion during sleep in patients with obstructive sleep apnea. This mechanical response largely reflects alterations in respiratory drive during periods of upper airway obstruction.

We were able to demonstrate that this response is influenced by age and sleep stage.[12] Although it is recognized that specific age or sleep-state related effects on upper airway muscle function may contribute to this observation, the role of these factors is likely to be modulated through their effect on respiratory drive. The role of respiratory drive in the mechanical response to upper airway occlusion was further illustrated by the relationship between respiratory effort and both hypoxic and hypercapnic ventilatory response.[13] Moreover, long-term continuous positive airway pressure (CPAP) treatment was shown to decrease respiratory effort, an effect that is likely to be related to changes in respiratory control.[14] From a more clinical perspective, we noted that the degree of respiratory effort developed during periods of upper airway obstruction

is an important predictor of the effective CPAP pressure, and that it plays a contributory role in the pathogenesis of excessive daytime sleepiness.[15,16]

## Conclusions

Measurement of esophageal pressure is recommended to exclude the presence of upper airway resistance syndrome in patients with excessive daytime sleepiness but without clear apnea, and to confirm the diagnosis of central sleep apnea syndrome. In addition, assessment of respiratory effort by means of esophageal pressure measurements is helpful for investigating the mechanical response to upper airway occlusion during sleep in patients with sleep-related breathing disorders.

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# SCREENING FOR OBSTRUCTIVE SLEEP APNEA SYNDROME

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## Introduction

The obstructive sleep apnea syndrome (OSAS) center at the University of Rome 'La Sapienza', which has been active since February 1996, has examined about two thousand patients for surgery. Most of these subjects present at our center complaining of snoring, and only some of these report the typical symptoms of OSAS. Initially, there was a ratio of seven to three between males and females presenting at the center, but during the last two years, since the risks connected with OSAS have been made public, and with the lessening of feminine modesty, this has changed to four to three. The ages of our patients vary quite considerably, with an average of about 49 years in males and 46 years in females. During the initial visit, diagnosis is made by means of anamnestic questionnaire, otolaryngological examination, and screening of personal details: pulsoximetry. At the same time, in each of the patient, we perform an audio-impedance examination in order to study the possible correlation between OSAS and hearing loss. In the cases in which it is difficult to identify the site of the obstruction, we request additional instrumental examinations such as CT and RMN. Allergic patients undergo an intradermo-reaction test (Prick test) and rhinomanometry in order to evaluate the degree of nasal obstruction.

At the second visit, based on the results of oximetry, the course to be followed is decided upon:

- if the result is negative: an aesthetic operation is carried out in order to diminish, and sometimes to eliminate, annoying snoring;
- if the result is positive: the patients undergo a night-time polysomnographic examination, which enables definitive diagnosis.

The day after this examination, the patients undergo cephalometry in order to pinpoint any other possible obstructive sites or maxillofacial alterations. The polysomnographic results are discussed during a further visit when, by means of re-evaluating the objective situation, the results of the questionnaire,

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and of the other investigations, we decide upon the type of therapy to be undertaken.

## Aim of this study

The aim of this study was to assess the sensibility and specificity of screening methods commonly used in the clinical practice of OSAS, by comparing the results obtained from polysomnographic examinations. Moreover, by means of an anamnestic questionnaire (most frequently the Epworth scale for drowsiness) and oximetry, we considered a new device, a portable sleep apnea screener, which approximately calculates the apnea/hypoapnea index (AHI) of patients.

This study originated because of practical problems: throughout the world (particularly in the USA), various categories such as truck drivers and pilots undergo periodic medical check-ups: evaluation of the attention threshold, tiredness, and diurnal drowsiness. For reasons of time and cost, it is too complicated to submit each of these subjects to a polysomnographic examination. Moreover, in many sleep centers there are added organisational problems due to the problems of recruitment of qualified personnel for carrying out the polisomnography. This causes rather long waiting lists. Moreover, the patients have problems in sleeping in a bed that is not theirs, which to a certain extent, alters the results of the night-time examination. Due to all these considerations, there is a need to look for methods that are sufficiently sensitive and specific to provide a clear idea of the clinical condition of the subjects before polysomnography takes place. The idea is to evaluate all the data obtained with the Epworth index, oximetry, and the dispensable sleep apnea screener, in order to calculate the specificity and sensibility of each investigation, and to compare these data with the results of polysomnography, to see whether these screening methods compare well with the actual diagnosis, and considering the economic implications of each method.

## Material and methods

The severity of OSAS was evaluated by means of various screening examinations, and diagnosis was made after the polysomnographic examination. For this study, we selected 114 patients whose first otolaryngological examination had taken place in our center, in order to make an homogeneous group and to exclude other pathologies. We analyzed:

- Forty-two subjects by screening with an anamnestic questionnaire which evaluated excessive daytime sleepiness (EDS) by means of the Epworth scale, with normal values being less than 10, borderline values from 8 to 10, and pathological values greater than 10.
- Forty-two subjects by screening with pulsoximetry; with pathological oxy-

hemoglobin saturation for values of less than 90% for more of the 10% of the recording time, or saturation falling to less than 75%, or more than 5-10 drops of oxyhemoglobin saturation per hour;

- Thirty subjects by screening with an orinasal digital fluxmeter apnea screener to estimate the value of the AHI; with a pathological AHI greater than 15.

After the entire group had been screened, the subjects underwent polysomnographic analysis to diagnose the following:

1. AHI;
2. the lowest recorded oxyhemoglobin saturation value during the entire examination (NADIR or LSAT: $SaO_2$ low);
3. the percentage of time that each subject spent during the night with an oxyhemoglobin value of less than 90%.

We then collated all the data and calculated the sensitivity and specificity of each screening method in relation to the results obtained during the polysomnographic study.

*Screening with the anamnestic test*

This questionnaire is the first test that the snorer undergoes in a sleep center. He completes it during his first medical examination and it is used as a subjective index in patient evaluation. The first sheet contains personal data, weight and height (in order to evaluate body mass index (BMI)). The questionnaire consists of 54 questions, divided into groups according to search aspects and an evaluation scale of diurnal somnolence: the Epworth scale (EDS: excessive daytime sleepiness). The snorer, preferably with the collaboration of his/her wife/husband, is urged to answer truthfully. A value is given to each group of questions, which enables us to select those subjects who more urgently need a polysomnographic examination.

The informative inquiry starts with a request for data about the condition of the snorer on his/her awakening and during the day:

1. Do you wake up tired in the morning?
2. Do you feel the need to sleep longer?
3. Do you have headache at your awakening?
4. Are you sleepy during the day?
5. Do you fall asleep easily during the day?
6. Have you ever fallen asleep during your daily activity?
7. Do you take frequent naps?
8. Do you have difficulty in concentrating on your tasks?

When many of the questions are answered positively, this guides us towards a probable diagnosis of OSAS or even gives us more information about the snorer's type of sleep, looking for a quality and/or a quantity inferior to what he needs.

Next, some questions are asked about his general condition, with regard to his ability to stay awake when he is driving:

9. Have you ever driven without remembering the way?
10. Do you have frequent road accidents?
11. Do you have any attacks of sleepiness when driving for distances longer than 200-300 km?

    In several studies, an increase in the frequency of road accidents caused by OSAS drivers has been demonstrated. In the USA, about 30% of drivers attribute their accidents to falling asleep while driving.

    The lack of sleep causes the person to find it difficult to relax in both the family environment and at work, and this often causes depression, emotional instability, and irritability. Some of the questions focus on these situations which can sometimes be underestimated, and are attributed to hard work or a particularly difficult period. The following questions are used for this purpose:
12. Do you have any relationship problems with your family, friends, colleagues?
13. Are you afraid that you have no clear ideas, that you are losing your memory?
14. Do your friends tell you that you are no longer the same person?
15. Do you get discouraged?
16. Are you irritable and nervous in the morning?
17. Have you noticed any changes of humor or behaviour?

    We now look into the possible presence of concomitant pathologies, into the health of the snorer, the usual blood-pressure values, the presence of any otolaryngological problems. We check whether the snorer is taking any drugs (*e.g.*, benzodiazepines) that could interfere with either his sleep period or with preservation of the muscular tone of the upper respiratory airways:
18. Do you wake up on average every night to go to the bathroom?
19. Have you ever urinated in bed?
20. Have you noticed a decrease of your libido?
21. Do you have any difficulty in accomplishing the sexual act?
22. Do you have difficulty in breathing through the nose?
23. Do you suffer from buzzing in your ears?
24. Do you have the feeling that you are hearing less in the last few years?
25. Do you feel any pain in your ears?
26. Do you suffer from vertigo?
27. Do you have difficulty in swallowing?
28. Do you ever have any regurgitation?
29. Has there been any alteration in your voice?
30. Do you have any respiratory disturbances?
31. Do you have high blood pressure?
32. Do you have any pain in your bones or joints?
33. Do you use any drugs (tranquillizers, sleeping drugs)?
34. Do you often have an alcohol drink before going to bed?
35. How many hours do you sleep every night?

    The following questions deal with problems that lead us to the diagnosis:

the characteristics of the sleep and the facility to fall asleep. We try to define the characteristics of patients' sleep by asking them whether they snore, have any apnea, or notice any aggravation of their condition when in a supine position.

36. Do you snore during sleep?
37. For how many years have you snored?
38. How would you define your snoring: light, moderate, or deep?
39. Is it intolerable for the person who sleeps next to you or in another room?
40. Do you snore all night long?
41. Is your snoring intermittent?
42. Do you only snore if you are sleeping in a supine position?
43. Do you have any pauses in breathing during sleep?
44. Do these pauses frighten your partner?
45. Is your sleep agitated?
46. Do you wake up on average every night?
47. Do you ever wake up with a sensation of disorientation?
48. Have you ever fallen out of bed?
49. Do you use more than one pillow to raise your head?

Finally, we ask for information about the diurnal symptomatology of our patients. We believe that OSAS mainly manifests with diurnal somnolence and a high facility for falling asleep; therefore, we evaluated EDS with the help of the Epworth scale, a graduated scale formulated by various psychologists in 1980, and published in 1991. Patients are asked to give a numerical value of from 0 to 3 to their ability (facility) to sleep in some daily situations:

- never = 0
- seldom = 1
- enough = 2
- very often = 3

Questions on the Epworth scale:

- being seated, reading a book or a newspaper;
- watching television;
- being seated in a public place;
- lying down and relaxing when the opportunity permits;
- being seated after lunch not having drunk any alcohol;
- in the car, when stopped in traffic for some minutes;
- in the car, as a passenger, travelling for more than an hour.

After considering the values resulting from this last group of questions, we subdivide the patients into:

1. not significant: a total index lower than 8;
2. borderline: a total index between 8 and 10;
3. significant: a total index higher than 10.

*Screening with pulsoximetry*

Pulsoximetry is a method that permits the non-invasive measurement of oxyhemoglobin saturation of the peripheral blood and of heart frequency: the device used is made up of a central unit and a peripheral one: a sensor. The central unit contains the hardware circuits that elucidate the data recorded, presenting these in numerical or graphic form. The sensor contains a piezoelectric crystal for data registration. There are several models available, according to the particular need:
*Sensor clips* (small rigid clips): these are placed on the finger of adult patients;
*Flexible sensors:* these are adaptable to each patient and are also placed on the finger;
*Children's sensors:* these have the same characteristics as flexible adult sensors, but are smaller and are placed on the big toe;
*Reflecting sensors:* these are for use on parts of the body with superficial blood vessels, but they do not guarantee the same performance as the other sensors.

These devices function on the principle that sending light at a determined wavelength (red or infrared), produced by a piezoelectric quartz, to the peripheral blood, and the reduced and conjugated hemoglobin having a different degree of absorption for the two kinds of light, the device placed on the opposite side is capable of establishing the percentage of oxyhemoglobin in the peripheral blood feeding the capillary vessel. The quantity of oxyhemoglobin, *i.e.*, the quantity of oxyhemoglobin conjugated, is proportional to the partial pressure of the oxygen ($pO_2$); at normal $pO_2$ (100 torr), the hemoglobin conjugated is called P 50.

At the same time, heart frequency is registered by the same sensor. This allows us to quantify the severity and intensity of the rhythm anomalies that we consider to be secondary to the night hypoxemia and of prime importance in OSAS symptomatology, as Guilleminault has also shown in his studies.

However, it should be remembered that there are some conditions that hinder the exact functioning of pulsoximetry; in particular: an area that is too shiny; patients who frequently change their position, suffer from anemia, have a low rate of peripheral perfusion, in whom the sensor is inadequate, and occasionally, those who have nails with thick skin and enamel.

*Screening with the digital fluxmeter apnea screener*

The digital fluxmeter apnea screener or Sleep Strip is the latest device to be invented for studying OSAS. The idea of this instrument is to check the aerial flux into the nose and mouth. It analyzes respiratory disturbances, taking into account remarks, acquisition, analyses, and the evidence of the data.

Flux signals are derived from three thermocouples in the same way as the standard sensors used for polysomnography in sleep laboratories, and they are filtered and digitized by an internal microprocessor. This microprocessor con-

tinually registers the signal, calculating its mean amplitude, the amplitude for each respiratory movement, and other parameters of the respiratory pattern. Episodes of apnea/hypopnea are registered for five hours, starting 20 minutes after activation of the device. The Sleep Strip is placed between the upper lip and the nose, a short time before going to sleep, with care being taken that the nasal sensors are folded in such a way that they can correctly register the thermic variations of air flux. The next day the patient returns the Sleep Strip to the center where the specialist can read the result on the display.

The total score is not the AHI, but the display is formed by six components used to read the values (placed in binary code 2-64), and two others to indicate, respectively, the technical validity and the presence of long apneas. The elements are shiny silver on new sensors, and some of them have become dark gray by the end of the examination. In order to calculate the score, together with the dark elements, it is enough to add the corresponding number, and to sum up.

When interpreting the result, it is important to remember that the technical validity indicator must be dark: this means that, during the first minutes of the examination, the flux signal is adequate; this indicates that the position is correct and that the device is functioning.

On the other hand, the long apnea element should not become dark; this would mean that the results are incorrect, because the signal was not controlled for at least 120 seconds, or because the patient removed the sensor, or because registration was lost during the night.

There are some contraindications to the application of the digital fluxmeter, among which are a few cases of nasal congestion or alterations in respiration.

*Polysomnographic evaluation*

Polysomnography is an examination that confirms the diagnosis of OSAS; it is complex, rather expensive and long, and requires at least one night in a sleep center and must be performed by qualified personnel. It is a diagnostic method based on the continuous recording, during night-time rest, of physiological parameters that enable apneas to be individualized. As is well known, during the night, cardiac, respiratory, and cerebral functions undergo important modifications. The purpose of this investigation is to record such changes and to evaluate whether they are physiological or are secondary to central pathology (*e.g.*, ictus, bulbopontine syndrome), to endocrine-metabolic pathologies, or to peripheral forms such as congenital or acquired obstruction of the superior respiratory airways.

The electroencephalographic (EEG), electro-oculogram (EOG), and electromyographic (EMG) examinations confirm the differential diagnosis of the different forms. The standard evaluation studies respiration, oximetry, cardiac frequency, body position, and the phenomenon of snoring.

For the respiration analysis, we employ two indexes: orinasal aerial flux and

chest movements. Aerial flux is the distinctive parameter for all forms of apnea; it is evaluated by means of a thermocouple, placed between the superior lip and the nostrils, which records the temperature gradient produced between the inhaled cool air and the expired warmer air. On the other hand, thoracoabdominal movements are measured by plethysmography; special elastic belts are used with thin tubes inside them. These tubes contain electric conductive material (mercury), which modifies their diameter during the inspiratory and expiratory excursions of the thorax and abdomen, thereby showing a sinusoidal type of signal. The absence of these movements points to apneas with a central origin; however, paradoxical movements are observed in cases of loss of the muscular tone of the diaphragm, of respiratory muscle accessories, or in obstruction of the superior respiratory airways.

Another important parameter is the oximetry that, across a piezoelectric crystal placed on the finger, measures the hematic saturation of oxygen ('reading' the ungual capillary bed) and cardiac frequency.

The position sensor shows the decubitus of the patient; this parameter is very useful for establishing whether the night-time symptomatology is always present, or if it manifests in particular conditions, *i.e.*, the supine position.

Finally, respiratory sounds can be recorded with the help of a microphone (sonograph) positioned at the jugulum, which recognizes the snoring phenomenon that is generally associated with and precedes episodes of apnea.

All these tools are part of standard polysomnography; in some cases, it is even possible to measure other parameters such as blood pressure and electrocardiogram. Blood pressure is important, despite the high incidence of hypertension in the subjects suffering from OSAS. It can be measured in a non-invasive way with tools consisting of a bonnet with muff which is placed on the distal phalanx of the patient's finger. When the bonnet is applied, the internal pressure is equal to that of the arterial vessel, reflecting the present pressure in the artery; obviously, such measurement is impossible in the subjects suffering from peripheric microangiopathies.

It is useful to remember that the partial pressure of oxygen ($PaO_2$) as well as that of carbon dioxide ($PCO_2$) can be measured transcutaneously in a non-invasive way with the help of an electrode heated to 43°C in order to dilate the vascular bed; the accuracy of this is closely related to the correct application of the sensor. There are no contraindications to polysomnography; obviously the more complete devices are not popular with patients, because it is difficult to fall asleep with all the sensors in place, and therefore, this makes the study practically impossible. However, equipment is now available, even for use at home, that enables OSAS to be diagnosed equally accurately with less parameters having to be recorded.

**Results**

We studied the group as a whole with the aim of evaluating the sensitivity and specificity of the screening methods (oximetry, EDS value, fluxmeter sleep apnea screener) compared to polysomnography (PSG), with particular emphasis on the advantages and disadvantages of the Sleep Strip in comparison to the other screening methods. It is useful to remember that:

- sensitivity is the ability of a test to produce positive results in subjects who are genuinely ill

  SENS = TP/(TP + FN) * 100
- specificity is the ability of a test to produce negative results in subjects who are not genuinely sick

  SPEC = TN/(TN + FP) * 100

It is preferable to use a high sensitivity test in cases of serious, curable illness, and when positive mistakes do not denote psychological burdens or economic damage for the patient; on the other hand, a test with elevated specificity is preferable in cases of serious, incurable illness, and when distorted positive findings would cause psychological and economic damage to the patient. Within these two parameters, we try to individualize the predictiveness of a diagnostic test, and for this reason, it was essential that the study group should include affected and normal subjects who could not be distinguished at the start.

*Results of excessive daytime sleepiness in 42 subjects*

*Classification according to the Epworth scale:*
>10 (significant EDS): *n* = 13
8-10 (borderline EDS): *n* = 11
<10 (EDS not significant): *n* = 18

*Patients with >10 EDS: n = 13*
mean age: 53 years
mean weight: 88 kg
positive polysomnography: 11 patients
negative polysomnography: 2 patients

*Patients with EDS 8-10: n = 11*
mean age: 54 years
mean weight: 82 kg
positive polysomnography: 6 patients
negative polysomnography: 5 patients

*Patients with <10 EDS: n = 18*
mean age: 59 years
mean weight: 81 kg
positive polysomnography: 10 patients
negative polysomnography: 8 patients

*Sensitivity* of the evaluation of EDS with the Epworth scale (in relation to PSG):
Tp/(Tp + Fn)*100 = 41%
*Specificity* of the evaluation of EDS with the Epworth scale (in relation to PSG):
Tn/(Tn + Fp)*100 = 86.7%

*Results of oximetric evaluation in 42 subjects*

Positive pulsoximetry: *n* = 27
Negative pulsoximetry: *n* = 15
*Patients with positive oximetry: n = 27*
mean age: 52 years
mean weight: 86 kg
positive polysomnography: 22 patients
negative polysomnography: 5 patients
*Patients with negative oximetry: n = 15*
mean age: 56 years
mean weight: 80 kg
positive polysomnography: 5 patients
negative polysomnography: 10 patients
*Sensitivity* of the evaluation by oximetry (in relation to PSG):
Tp/(Tp + Fn)*100 = 81.5%
*Specificity* of the evaluation by oximetry (in relation to PSG):
Tn/(Tn + Fp)*100 = 66.7%

*Results of evaluation with the fluxmeter sleep apnea screener in 30 subjects*

Positive Sleep Strip: *n* = 19
Negative Sleep Strip: *n* = 11
*Patients with positive Sleep Strip: n = 19*
mean age: 50 years
mean weight: 81 kg
positive polysomnography: 12 patients
negative polysomnography: 7 patients
*Patients with negative Sleep Strip: n = 11*
mean age: 53 years
mean weight: 78 kg
positive polysomnography: 4 patients
negative polysomnography: 7 patients
*Sensitivity* of the evaluation with the fluxmeter sleep apnea screener (in relation to PSG):
Tp/(Tp + Fn)*100 = 75%
*Specificity* of the evaluation with the fluxmeter sleep apnea screener (in relation to PSG):
Tn/(Tn + Fp)*100 = 50%

## Discussion and conclusions

This study aimed to discover which of the OSAS screening methods was more predictive in diagnostic terms. We also attempted to underline the advantages and disadvantages of the new orinasal digital fluxmeter sleep apnea screener compared to traditional investigations (oximetry, Epworth scale).

We focused not only on purely clinical aspects, but also on the costs and realization times of the different approaches. The necessity of research of this kind originates from practical problems, for example, the analysis, in a limited time, of large groups of persons; each year in the USA, truck drivers, pilots, car drivers, and other categories of workers routinely undergo these examinations in order to study diurnal drowsiness, the decrease of the attention span, and the symptomatology of OSAS in general.

From the anamnestic questionnaire study, we noted that the Epworth scale has highly satisfactory specificity (86.7%), but rather low sensitivity (41%). It has the advantage of being almost cost-free, and provides immediate results, but it relies on the answers of the subjects, however truthful they may be. It is easy for the subjects to think that they are answering all the questions honestly, and they are not always totally aware that they are sometimes hiding at least part of the truth for risk of losing their job.

Oximetry has always been considered the most valid screening test, and it gives independent results for sensitivity (81.5%) and specificity (66.7%). Its principal limitations are its initial cost, the costs of its operation, and the long waiting lists it incurs. For example, from the point of view of time, a sleep center such as 'La Sapienza' which, since February 1996 has performed about 1700 examinations, would not be able to carry out a screening program for a large airway company. We are restricted by the cost and time needed to search for a teaching method that is easier to realise, but just as reliable. In our view and in normal conditions, oximetric screening would seem to provide the most valid results.

The orinasal digital fluxmeter sleep apnea screener has mainly provided satisfactory results, with a sensitivity of 75% and a specificity of 50%. But, from the start, it should not be forgotten that some devices did not provide reliable values when they recorded apneas of longer than 120 seconds. It is a screening method that is easy to realise, even in large groups of persons, and it is also comparatively economical since it does not involve any operating expenses. However, it does not provide us with enough data to exempt patients from a possible polysomnographic examination. Compared to the Epworth scale, the orinasal digital apnea screener has the advantage of being able to provide more objective results, independent of the responses of the patient. It has lower specificity, which does not enable unaffected subjects to be identified instantly, but it has greater sensitivity, which is the indication for polysomnography. Compared with oximetry, both its validity indexes are inferior, and moreover, it is unable to provide enough results; with oximetry, from analysis of the pattern,

it is possible to obtain an idea of the severity of OSAS in a particular patient, while with fluxmetry screening we can only obtain an estimate of the quantity of apnea/hypopnea which, compared to polysomnography, does not always correspond to the actual AHI.

The clinical evolution from simple rhoncopathy to OSAS, the onset of a greater number of diurnal symptoms, the consequences of the pathology, all impose the necessity for a detailed diagnosis and for rapid therapeutic planning. The screening methods analyzed by us, if used properly, are capable, from the outset, of allowing a detailed approach in more serious cases, as well as the follow-up of subjects who are considered to be at risk for the pathology.

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# INDIVIDUALIZATION OF THE SITES OF OBSTRUCTION

## Role of the otorhinolaryngologist

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### Introduction

Simple snoring, the upper airways resistance syndrome (UARS) and obstructive sleep apnea syndrome (OSAS) are all linked to obstructions of the upper aerodigestive tract (VADS), which can be of many sizes up to complete obstruction, which can lead to the total arrest of breathing. There can be many sites of obstruction, differing in size and importance, in the same subject.

In a patient in whom OSAS or habitual snoring has been diagnosed by polysomnography, the precise location of the site or sites of obstruction is fundamental in order to plan the most suitable therapeutic treatment.

It is a well-known fact that inaccurate diagnosis led to many unsuccessful cases of ronchosurgery or OSAS surgery in the 1980s and 1990s. In fact, too much importance was attached to the site of the retrovelar obstruction, while other sites which interacted with the former, and which often had a more important role, were neglected.

Therefore, it is imperative to use the skills of an otorhinolaryngologist during the diagnosis in order to enable specification of the site and size of the obstruction in the VADS in static and dynamic conditions, as well as of the origin of OSAS or of simple habitual snoring, also with reference to the variability of individual anatomical conditions. This is decisive for a diagnosis geared towards an individual patient.

Otorhinolaryngological (ORL) examination is fundamental in the diagnosis that precedes any OSAS or ronchosurgery, and should include anamnesis and a detailed, objective examination of the state of the nasal fossae, rhinopharynx, velum and retrovelar site, oropharynx, and particularly the tonsillar pilae (pillars), lingual basis (base), and larynx.

Thereafter, the specialist can resort to some simple and cheaper instrumental

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analyses that allow his or her diagnosis to be confirmed or specified: rhinomanometry and nose-pharynx-larynx videofibroendoscopy with a retrovelar and retrolingual Müller maneuver. More complex and expensive analyses (TC, cine-TC, RMN or Rmd, somnusfluoroscopy) are used in selected cases.

## Sites of obstruction

In the pathogenesis of UARS and OSAS, a fundamental role is attached to obstruction of the VADS, induced anatomically and functionally.

The anatomical causes for stricture of one or more sections of the VADS frequently act in the rhinopharynx, oropharynx or hypopharynx, where, especially in serious obesity, there can be an abnormal amount of peripharyngeal adipose tissue and/or hypertrophy of the soft tissue of a pharynx with reduced elasticity. A very important site is the soft palate together with uvula, which can gain weight, loose elasticity, and swell due to hypertrophy, adipose tissue mass, chronic inflammatory edema, etc. Other anatomical causes commonly seen are hypertrophy of the palatine tonsils and, occasionally, of the lingual tonsils, and hypertrophy of the lingual base and macroglossia. Therefore, there are less frequent anatomical conditions, such as the position of the hyoid bone being lower, that cause retroposition of the tongue, or other facial bony anomalies that cause micrognatia or retrognathia.

From a functional point of view, an increase in total activity of the genioglossus muscle, responsible for pharyngeal dilatator activity, has been observed in these patients in wakefulness.[1] This muscle causes the walls of the pharynx from collapsing. However, during sleep, due to the physiological decrease in muscular activity of the VADS, it can no longer carry out this function. Therefore, the site of obstruction is hypopharyngeal and, in this case, has a primarily functional cause.

Riley *et al*. have suggested a simple classification according to the site of the obstruction, as follows:[2]

- Type I: obstruction at an oropharyngeal level
- Type II: obstruction at an oropharyngeal and hypopharyngeal level
- Type III: obstruction at a hypopharyngeal level

Friedman *et al*.[3] have expanded the role of the simple physical examination, and starting from parameters used by anesthesiologists to identify patients likely to have difficult intubation, have suggested a rather simple methodology that also uses the results of polysomnography to ascertain the clinical predictors of obstructive sleep apnea. Their starting point is physical examination by visualization of the oropharynx: the patient is evaluated with open mouth but without protrusion of the tongue, using a modification of the Mallampati technique (MMP):

- grade I: tonsils, pillars, and soft palate are visible;
- grade II: uvula, pillars, and upper pole are visible;

- grade III:only part of the soft palate is visible; tonsils, pillars, and base of the uvula cannot be seen;
- grade IV: only the hard palate is visible.

Other parameters in the physical examination are thyroid-mental distance (TMD), hyoid-mental distance (HMD), and tonsil grades:

- grade 0: patient has had a tonsillectomy
- grade I: tonsils are in the tonsillar fossa
- grade II: tonsils are visible behind the anterior pillars
- grade III: tonsils extend three quarters of the way along the midline
- grade IV: tonsils completely obstruct the airway

These data are then correlated with the body mass index (BMI) and the respiratory disturbance index (RDI) collected by polysomnography.

From a simple anatomical point of view, the site of the obstruction can be placed at different VADS levels, as follows:

- nasal fossae
- rhinopharynx
- retrovelar region
- oropharynx
- base of the tongue

*Nasal obstructions*

After careful anamnesis, the specialist turns his attention to examining the different sections of the nasal fossae (Cottle's areas):[4]

1. *Vestibular area:* it must be possible to observe the endonasal portion of the lobulus, from the external nostril to the lumen nasi, which is the junction line between the caudal edge of the triangular cartilage and the cephalic edge of the alar one.
2. *Valve area:* the area of the so-called nasal valve must be examined, which, in Mink's classic definition, is bound by the cartilage septum and the caudal edge of the triangular cartilage, and also includes the fibro-adipose 'empty triangle' and the lower edge of pyriform opening.[5]
3. *Attic area:* this area is less important because of nasal perviousness.
4. *Front area of the turbinates:* examination of this area is very important, as well as the sinusal ostia and the tuberculum septi or septal cavernous body, which can sometimes be increased enough to reduce access to the median meatus and olfactory cleft.
5. *Back area of the turbinates:* examination of this area should always include preliminary decongestion and is often completed by videoendoscopic examination.

All possible causes of obstruction should be investigated by ORL examination:

- deviation of the nasal septum (particularly of areas 4 and 5)
- hypertrophy of the turbinates or moriform degeneration

- other mucosal diseases (allergic, vasomotor, iatrogenic, infective rhinitis, crustal atrophic rhinitis, etc.)
- congenital or acquired anomalies of the nasal valve
- stenosis of endonasal synechiae
- nasal polyps
- tumors
- cystides
- reduced craniofacial development due to congenital disease

*Rhinopharyngeal obstructions*

Rhinopharyngeal examination is performed by endoscopy to investigate the possible causes of obstruction. This site of obstruction is particularly important in children, because of the hypertrophy of the adenoids often seen in them. Less frequent, possible choanal unilateral atresia, which can go unobserved, has to be searched for between the nose and the rhinopharynx, in area 5, in case of anamnestic relief of the nasal obstruction without confirmation in areas 1-4. In bilateral forms, due to the manifest symptomatology, early diagnosis can be made soon after birth. In exceptional cases, rhinopharyngeal stenosis can have a congenital origin. In adults, acquired rhinopharyngeal stenosis can be caused by the proliferation of neoplastic tissue or by cicatricial retractions due to adenectomy, etc.

*Retrovelar obstructions*

The retrovelar space can easily be examined using videofibroendoscopy, and the stenosis can be of cicatricial origin due to velopharyngeal synechia or concentric cicatrization, uvulopalatopharyngoplastic (UPPP or UP3) complications or, more often, laser-assisted uvuloplasty (LAUP). In these cases, planning the surgical correction requires careful endoscopic study in order to reduce the already high risk of the relapse of the attempted correction of the cicatricial stenosis. The presence of any uvulovelar hypertrophy with or without veloptosis should be carefully estimated, together with its size, or in static conditions, whether there is any congenital retrovelar narrowing. Dynamic evaluation of this space is carried out using a retrovelar Müller maneuver, performed face upwards.

*Oropharyngeal obstructions*

The narrowest point of this site is the faucial isthmus, limited by the velum upwards and the lingual ‘V’ downwards. At the side corners of the pharynx, masses of lymphatic tissue can be found which occasionally causes obstruction or narrowing of the side walls of this space. A frequent cause or joint cause of obstruction is tonsillar hypertrophy or hyperplasia, so this must be considered,

especially when the tonsils are intermediate in size and could easily deceive a careless observer. We have already seen how unsuccessful surgical operations are in treating the palate alone, and where tonsillectomy was not considered. Macroglossia should be evaluated together with the lingual base region.

*Retrolingual obstructions*

Static evaluation of the retrolingual space is usually directed to all those lymphatic structures called 'tonsilla linguale', which are very developed in children but veer towards atrophy in adults. In some subjects, especially ronchopathics, the presence of hypertrophic lymphatic tissue at the base of the tongue, specifies obliteration of the glosso-epiglottic space and narrowing of the retrolingual space, which, together with the collapse of the base of the tongue during sleep, represents a very serious obstruction.

Only an experienced specialist can evaluate this space, because there is no absolute guarantee of a precise method:

- indirect laryngoscopy can mislead an inexperienced examiner because the front traction of the tongue determines the unnatural advance of its base; videofibroendoscopy with the patient face upwards is more reliable;
- the retrolingual Müller maneuver, as with the retrovelar one, is more or less influenced by the cooperation of the patient, and this is why you have to consider it *cum grano salis*;
- cranial lateral teleradiography can give different outlines, according to how the head is inclined.

Finally, a static and dynamic evaluation of the retrolingual space is very important in planning the treatment of OSAS, but the otologist must be very careful and experienced because he must make use of data provided by different methodologies.

**Imaging and endoscopy**

Modern techniques for imaging the cervical-cephalic area and endoscopic examination of the VADS are extremely useful and important in the study of patients with OSAS, because they can provide very useful information regarding the site and size of an obstruction. Their use cannot be extended to all patients, but ORL specialists will choose only those cases in which they cannot make a diagnosis using traditional semiological techniques. Their integrated use is very important both in the introductory stages of planning a surgical operation, and in the later evaluation if it fails, in this case in order to be able to adopt better corrective procedures.

*Computerized tomography*

Conventional computerized tomography (TC), carried out during a normal breathing cycle and during forced inspiration, shows:

- anatomical anomalies of the cranial-cervical bony structures
- pathologies of the facial mass
- pathological tissue obliterating the rhinopharynx
- hypertrophy of the uvula
- size of the palatine tonsils
- size of the lingual tonsils
- measurements of the different sections of the pharyngeal lumen at different levels

Horner *et al*.[6] carried out conventional TC in patients with OSAS, both during sleep and wakefulness, and using axial projections, demonstrated that obstruction of the VADS is provoked by the approach of the soft palate and the base of the tongue to the back wall of the pharynx, and by the concentric collapse of the pharyngeal lumen. However, the lack of sagittal sections impedes a comprehensive evaluation in the lateral perspective, and it is impossible to check whether the decrease in the pharyngeal lumen depends on the size of the tongue, on mandibular dimorphism, or on the anomalous position of the hyoid bone.

Spiral TC has made it possible to go beyond some of the limits of conventional TC, because it restricts the results caused by breathing and swallowing movements, and gives a good total view of the VADS.

Tridimensional TC, through which images obtained by spiral TC are reconstructed by means of sophisticated software, is only suitable for patients with craniofacial malformations, because it is a complex, slow, and expensive technique. It is important when planning operations for maxillary and mandibular advancement. However, neither is it able to indicate soft parts, particularly any peripharyngeal adipose tissue.

Cine-TC, which permits analysis of the VADS during breathing both in sleep and wakefulness, is a complex, expensive method, which would expose the patient to prolonged radiation. It is only used in a research context.

*Magnetic resonance*

Magnetic resonance (MR) enables good evaluation of the peripharyngeal soft tissues with highly detailed anatomical images of any projection: axial, coronal and, most usefully, sagittal. In this case, too, the problem is how to interpret images obtained during inspiration superposed on those obtained during expiration. Another limitation is the serious obesity of many patients with OSAS. MR particularly shows:

- breadth of the aerial space at different levels

- volumetric and tonal alterations of the soft palate, base of the tongue, and lateral pharynx walls
- tongue and oral floor morphology and relationship with the mandible and hyoid bone
- grade of hypertrophy and adipose infiltration in the intrinsic tongue muscles
- amount of adipose infiltration in the peripharyngeal spaces

In patients with OSAS, dynamic MR enables a dynamic record of the obstructive episode to be made, at an oro/hypopharyngeal level. However, it is a very expensive examination, and even if it does not cause long exposure to radiation, it is reserved for selected cases only, particularly those OSAS patients affected by a pure dynamic form, in whom it has not been possible to find the site of the obstruction.

*Endoscopy with stiff fiberoptics*

A 0° or 30° angulation instrument can complete the tasks of the objective ORL examinations performed previously. With 30° optics, it is also possible to see the back wall of the soft palate.

*Endoscopy with flexible fiberoptics*

By means of this instrument, best connected to a videorecording system by a TV-cam, careful examination is possible of earlier detected, anatomical anomalies, with the examination being extended to the entire VADS. By means of rhinopharyngeal laryngoscopy, the following can be visualized:

- back wall and size of the soft palate
- size and relationships of the uvula
- base of the tongue and lingual tonsils (examined in normal conditions and without anterior traction of the tongue, which makes indirect laryngoscopy unreliable)
- dynamic tests during oral or nasal breathing
- snoring test
- possible velar surplus during phonation (the patient is made to pronounce 'ké')

Particular mention must be made of the study of hypotonicity of the pharyngeal walls and soft palate velum with the Müller maneuver[7] under fiberendoscopic control. The patient, first seated and later face upwards, forcibly inspires many times with a closed nose and mouth, while, for the purposes of the study, the examiner inserts the exploring fiberoptic at different levels of the aerial via:

- a retrovelar site
- a retrolingual site
- the laryngeal aditus

The negative pressure, artificially induced by means of this very simple maneuver, reveals the possible muscular hypotonicity and the collapsibility of

the pharyngeal walls, and therefore it allows the ORL specialist to discover and record pharyngeal phenomena under dynamic conditions.

A classification by grades of pharyngeal obstruction has been proposed according to the amount of narrowing of the breathing space recorded during the Müller maneuver:

+1 minimum concentric movement of the pharyngeal walls
+2 a 50% decrease of the cross-section area
+3 a 75% decrease of the cross-section area
+4 total occlusion of the pharyngeal lumen

The Müller maneuver is not totally effective because it gives false positives or false negatives in about 50% of cases. Therefore, it should be evaluated together with other data during the ORL examination. In fact, it creates a non-physiological situation, and can lead to overestimation of the pharyngeal effects of the artificially induced depression, and to underestimation in those patients who cannot correctly perform the forced inspiration. To assist in the research and with some difficulty, a videoendoscopic record was also made during sleep, and the results can be compared with those of dynamic MR.

## Rhinomanometry and acoustic rhinometry

Rhinomanometric and rhinometric examinations are useful aids for the ORL specialist when the site of the nasal obstruction needs to be further examined after an objective ORL examination has been performed.

Rhinometry is a technique that allows the perviousness of nasal fossae to be evaluated by measuring the aerial flux and pressor gradient between the nostril orifices (anterior nasal pressure) and rhinopharynx (back nasal pressure). The patient notes inspiration and expiration during spontaneous breathing, by means of a mask on the face. In clinical practice, anterior active rhinometry is commonly used, because it allows nasal flux to be recorded in a single nostril, while the back pressure is relieved by a small pipe applied to the non-breathing nostril, where pressure is conventionally the same as that in the choanae. The examination is performed in basal conditions and after decongestion, sitting and face upwards (positional test), or after allergenic stimulation (nasal provocative test). Therefore, it is possible to confirm and document whether the obstruction is of anatomical or functional origin.

The most modern technique of acoustic rhinometry allows us to evaluate the anatomical geometry of nasal fossae. By connecting a suitable pipe to an olive, which is then inserted into the nostril, an acoustic signal of 150-10,000 Hz is transmitted, and the differences noted in the impedance offered by different sectors of the nasal fossa, are processed by relevant software. The results are reported on a graph where the different sections of the nasal cavity can be indicated, expressed in square centimeters relating to the distance from the nostril.

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# CEPHALOMETRIC VARIABLES IN THE DIAGNOSIS OF OBSTRUCTIVE SLEEP APNEA SYNDROME

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## Introduction

Obstructive sleep apnea syndrome (OSAS) is a clinical condition characterized by blood oxygen desaturation and nocturnal apnea related to pharyngeal obstruction. It is associated with a number of signs and symptoms, such as dry throat, headache, excessive daytime sleepiness, poor memory, and depression.[1] Anatomical features have also been reported, such as short cranial base, retrusion and/or clockwise rotation of the mandible, reduced sagittal dimension of both jaws, low position of the hyoid bone, and narrow airway space, but evidence of a direct relationship between craniofacial morphology and OSAS has not been clearly found in the literature.[1-8]

The aim of the present study was to investigate the craniofacial structures, airway depth, soft tissue morphology, and hyoid bone position in a group of OSAS patients, and to compare these patients with non-snoring subjects with harmonious facial type, in order to determine the most significant parameters for the cephalometric diagnosis of OSAS.

## Subjects and methods

The sample group consisted of 120 adults (90 males and 30 females) with a polysomnographic diagnosis of OSAS, aged from 45 to 78 years. The control group comprised 60 non-snoring subjects (40 males and 20 females) with ideal occlusion, harmonious facial type and normal airway patency.

Standard lateral skull radiographs were taken in the upright position with teeth in occlusion and relaxed musculature. Edentulous patients and subjects with their posterior teeth missing were excluded from the cephalometric analy-

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sis. On the lateral skull radiographs, the following cephalometric variables were measured:

*Skeletal variables*
- SNA (maxillary prognathism)
- SNB (mandibular prognathism)
- ANB (sagittal basal relationship)
- NSBa (cranial base angle)
- NL-NSL (maxillary inclination)
- ML-NSL (mandibular inclination)
- ML-NL (vertical basal relationship)
- N-Sp' (upper anterior facial height)
- Sp'-Gn (lower anterior facial height)
- ANS-PNS (hard palate length)
- Go-Gn (mandibular body length)
- Cd-Go (mandibular ramus length)

*Pharynx morphology*
- paw1-PNS (upper pharynx width)
- paw2-t (middle pharynx width)
- paw3-tb (lower pharynx width)
- PNS-E (pharynx length)
- PNS-Aa (pharynx 'osseous' width)

*Soft tissue variables*
- soft palate length
- soft palate thickness
- tongue length
- tongue height

*Hyoid bone position*
- ML-h (vertical hyoid bone position)
- Rgn-h (distance hyoid bone – mandibular symphysis)
- C3-h (distance hyoid bone – third cervical vertebra)

The method error included double measurements of all cephalometric variables, and was calculated according to Dahlberg. It varied from 0.20-0.56° for angular variables and from 0.23-0.51 mm for linear measurements; therefore, it was acceptable.

The two-tailed Student *t* test was performed to determine whether there were significant differences between the two groups for each variable.

## Results

The results are presented in Tables 1 and 2.

In the OSAS group, maxillary and mandibular prognathism were significantly decreased (SNA: $p < 0.05$; SNB: $p < 0.001$), the ANB angle was in-

*Table 1.* Skeletal variables in the OSAS patients and the control group (Student's *t* test)

| | *OSAS* | | *Control* | | |
|---|---|---|---|---|---|
| | *x* | *s* | *x* | *s* | *t* |
| SNA | 80.48 | 4.15 | 82.07 | 3.03 | -2.50* |
| SNB | 76.80 | 4.33 | 79.97 | 3.38 | -4.70*** |
| ANB | 3.68 | 2.62 | 2.10 | 1.51 | 4.13*** |
| NSBa | 129.97 | 5.22 | 129.81 | 5.21 | 0.16 |
| NL-NSL | 9.39 | 4.16 | 8.47 | 3.02 | 1.44 |
| ML-NSL | 33.83 | 7.44 | 30.01 | 4.82 | 3.43*** |
| ML-NL | 24.49 | 7.08 | 21.54 | 4.42 | 2.81** |
| N-Sp' | 58.15 | 3.72 | 55.61 | 3.12 | 4.24*** |
| Sp'-Gn | 73.89 | 6.21 | 68.53 | 5.41 | 5.31*** |
| ANS-PNS | 54.63 | 5.53 | 56.41 | 4.46 | -2.33* |
| Go-Gn | 75.84 | 6.07 | 77.50 | 5.88 | -1.61 |
| Cd-Go | 66.03 | 6.51 | 64.20 | 6.12 | 1.70 |

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

*Table 2.* Pharynx morphology, soft tissue variables, and hyoid bone position in the OSAS patients and the control group (Student's *t* test)

| | *OSAS* | | *Control* | | |
|---|---|---|---|---|---|
| | *x* | *s* | *x* | *s* | *t* |
| Paw-PNS | 25.69 | 4.09 | 26.81 | 4.44 | -1.58 |
| Paw2-t | 18.81 | 4.35 | 18.88 | 4.72 | -0.10 |
| Paw3-tb | 11.91 | 3.62 | 11.94 | 4.20 | -0.05 |
| PNS-E | 81.10 | 8.58 | 67.75 | 6.84 | 9.82*** |
| PNS-Aa | 36.52 | 4.69 | 35.11 | 4.48 | 1.80 |
| Palate length | 43.29 | 5.60 | 34.47 | 4.06 | 10.19*** |
| Palate thickness | 9.97 | 2.39 | 7.64 | 1.63 | 3.88*** |
| Tongue length | 90.74 | 7.04 | 78.26 | 5.99 | 11.08*** |
| Tongue height | 38.31 | 3.74 | 37.32 | 4.27 | 1.46 |
| ML-h | 23.89 | 6.44 | 12.10 | 4.93 | 11.84*** |
| Rgn-h | 46.03 | 6.41 | 39.28 | 5.93 | 6.31*** |
| C3-h | 41.72 | 5.25 | 37.03 | 5.20 | 5.23*** |

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

creased ($p < 0.001$), and the ML-NSL and NL-ML angles were larger ($p < 0.001$) than in the controls; Sp' and Sp'Gn were longer ($p < 0.001$), while the length of the hard palate was slightly less (ANS-PNS: $p < 0.05$).

No differences were found between the two groups with respect to airway width, while the pharynx appeared to be significantly longer ($p < 0.001$). The soft palate was elongated and thickened (SNP-P: $p < 0.001$; MPT: $p < 0.001$), and the tongue was elongated (E-tt: $p < 0.001$).

The distance from the hyoid bone to the mandibular plane was significantly greater in the OSAS group ($p < 0.001$), as well as the Rgn-h and C3-h distances ($p < 0.001$).

## Discussion

Various characteristic features in the craniofacial morphology of OSAS patients have been reported in several cephalometric studies:[1,2,4,5,7,8] the cranial base appears to be shorter than in control groups; the sagittal dimension of both jaws is smaller and is in a more retrognathic position; the height of the lower face is increased, as the mandible tends to be rotated posteriorly. Moreover, the chin and tongue are retruded, the soft palate is elongated, and the upper airway space is narrowed.

It has been suggested that retropositioning of the facial skeleton, together with fatty deposits in the pharyngeal tissues, may lead to a reduction in the upper airway space.[2,3]

In our study, significant skeletal differences were found between the two groups: the OSAS patients had a lower degree of maxillary and mandibular prognathism and a more open vertical interbasal relationship compared to the controls. The mandible seemed to be posteriorly displaced and posteriorly rotated in the OSAS group. This is a characteristic of mouth-breathers and, in fact, mouth breathing has been found in those OSAS patients who are heavy snorers.

The oropharyngeal airway was only slightly reduced compared to the control group, and the difference was not significant. The hyoid bone was significantly lower, reflecting a low tongue position in the OSAS group.

These findings are in good agreement with another study that showed that the skeletal variables with the strongest diagnostic accuracy in OSAS were mandibular prognathism (SNB) and inclination (ML-NSL).[6] Sagittal and vertical discrepancies are important in the relationship with OSAS, but hyoid bone position and vertical dimension of the pharynx (PNS-E) appear to be the most important parameters when making a cephalometric diagnosis of OSAS.

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# THE CLINICAL ASSESSMENT OF DAYTIME SLEEPINESS IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA

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## Abstract

All patients coming to a sleep center should have a quantitative assessment of their daytime sleepiness. This has proved to be more difficult than was thought in the past. Daytime sleepiness is defined here as sleep propensity – how likely the subject is, relative to other people, to doze off while engaged in particular activities. The nature of the subject's activity (*e.g.*, whether standing up or lying down) has a profound influence on sleep propensity at a particular time, so sleepiness can only be measured in relation to specific postures and activities. Different categories are needed to describe sleepiness under different circumstances and time frames. These include the subject's instantaneous sleep propensity (ISP) at a particular time, his situational sleep propensity (SSP) when in the same situation repeatedly, and his average sleep propensity (ASP) across a variety of activities in the course of his daily life. Several objective and subjective methods for measuring a subject's ISP, one or more SSPs, or ASP, are described. Although, in the past, many people believed that the Multiple Sleep Latency Test (MSLT) is the gold standard, recent evidence raises serious doubts about its accuracy as a measure of ASP. The Maintenance of Wakefulness Test (MWT) is the preferred objective method, but it is time-consuming and expensive. The Epworth Sleepiness Scale (ESS) is simple and cheap to use. It has been validated, has very good psychometric properties, and has been translated into many languages. However, it is based on subjective reports that have the potential for falsification and bias. It appears that different SSPs in the same subject are not always closely correlated because there are subject x situation-specific interactions, depending on how each subject responds to each situation in which sleepiness is measured. We do not have a gold standard test for ASP. The severity of obstructive sleep apnea (OSA) is only weakly correlated with any measure of sleepiness used so far. Nevertheless, patients with OSA, as a group, have higher than normal ASPs which can be reduced by successful treatment.

## Introduction

Excessive daytime sleepiness (EDS) is a common complaint among patients who present to sleep centers, including those with obstructive sleep apnea (OSA).

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How best to quantify their EDS is still a vexing question.[1,2] So, too, is the relationship between the severity of OSA and EDS.[3] There appear to be several reasons for this. One is the lack of clear definitions of terms such as sleepiness and fatigue, which are often used interchangeably when they ought not to be. Sleepiness is defined here as sleep propensity – the tendency or likelihood, under a given set of circumstances, of making the transition from wakefulness, via the drowsy state, to sleep. From a practical point of view, the relevant circumstances are usually those encountered in daily life when the subject's intention is to remain awake as, for example, when driving a car. The currently accepted conceptual framework within which to consider sleepiness appears confused and is contributing to our problems.[1] There is little recognition that several factors other than a variety of sleep disorders influence a subject's sleepiness, although not all the mechanisms may yet be clear. These factors are in addition to the time of day (process C) and the duration of prior wakefulness (process S) that are quite well understood.[4] Among other variables are the subject's posture and activity, both physical and mental, and the characteristics of the environment at the time.[5] Johns has called these characteristics of the test situation its somnificity, and has produced an ordinal scale of somnificities for several different situations.[6] We cannot assume that sleepiness is like body height, *i.e.*, similar under whatever circumstances it is measured. On the contrary, it appears that we cannot directly quantify sleepiness without reference to the situation in which it is measured. To complicate matters, there also appear to be subject x situation-specific interactions that modify at least some subjects' responses to a particular situation in ways that are not predictable.[5,6] In addition, there are substantial differences in sleepiness, even between normal subjects, which may be due to a psychophysiological trait, partly inherited.[7]

The assumptions underlying tests purporting to measure sleepiness have seldom been questioned or made explicit. The validity, reliability, and accuracy of many of those tests has never been adequately documented. Even the Multiple Sleep Latency Test (MSLT)[8] which, for the past 20 years, many people believed to be the gold standard, did not have its reference range of normal values published until recently (see below). When it did, the MSLT was found to be wanting as a gold standard, based on the inadequacy of its sensitivity and specificity in distinguishing untreated narcoleptic patients, who by definition have EDS, from normal subjects.[9] At different times, we may want to know how sleepy a person is in daily life, whether he is too sleepy to drive a vehicle at a particular time, or by how much his sleepiness has changed after treatment of his sleep disorder, such as with nasal continuous positive airway pressure (CPAP) treatment of OSA. Whatever tests of sleepiness are used under those different circumstances, they should all have a common frame of reference conceptually, and we should know how one set of results relates to another. Currently, it is assumed by most people that, if a subject is relatively sleepy under one set of circumstances, he should also be relatively sleepy under a

different set. This is evidently not always so (see below). Several new categories of sleepiness may help to elucidate this problem, as follows:

*Instantaneous sleep propensity (ISP)*: a subject's sleepiness at a particular time, whatever the circumstances. The ISP varies widely with posture and activity, the time of day, the duration of prior wakefulness, etc. It can change rapidly, decreasing over periods of seconds and increasing somewhat more slowly. It increases progressively with the level of drowsiness.
*Situational sleep propensity (SSP)*: a subject's usual sleepiness in the same situation repeatedly, such as sitting and reading. There would be as many SSPs for each subject as there are different situations in which to measure sleepiness.
*Average sleep propensity (ASP)*: a hypothetical construct based on a subject's average level of sleepiness when engaged in a variety of different activities in situations that he usually meets in daily life. The ASP usually remains constant, but it may change, for example, with the start of a sleep disorder, or with its successful treatment.

Within this context, EDS would occur when a subject's ISP exceeded a critical level that made him temporarily unfit to perform a task that most alert subjects could perform reliably. This might be called occasional EDS. It would be caused by circumstances that were unusual for the subject, such as after missing a night's sleep. In contrast, chronic EDS would be present in a subject whose ASP was perpetually higher than normal and who habitually dozed off in situations in which normal subjects usually do not. The relevance of these categories of sleepiness will be illustrated when considering the tests used for measuring sleepiness (see below).

## Tests of sleepiness

There are many methods for measuring sleepiness, some of which have been widely used, and others which have been proposed (Table 1). The list of tests in Table 1 is not exhaustive. They can be divided into two broad categories, objective and subjective, with subdivisions in each.

One group of objective tests measures how rapidly the subject falls asleep in the sleep laboratory during the day. These tests are based on what appears to be a reasonable premise, that the quicker we fall asleep, the sleepier we must be.

### *Multiple Sleep Latency Test*

The MSLT measures how long it takes the subject to fall asleep (the sleep latency in minutes) after instructions to try and sleep after lying down for 20 minutes at two-hour intervals during the day, while polysomnographic record-

*Table 1.* Different kinds of tests of sleepiness

| |
|---|
| *Objective tests of sleepiness* |
| *Sleep latency* |
| Multiple Sleep Latency Test (MSLT) |
| Maintenance of Wakefulness Test (MWT) |
| *Other parameters* |
| EEG frequency, power |
| pupillometry |
| eye movements (saccades, slow eye movements, tracking) |
| eyelid movements (blinks, drooping) |
| evoked potentials (visual, auditory) |
| performance tests (reaction time, divided attention tasks) |
| *Subjective tests of sleepiness* |
| *Feelings, symptoms* |
| Stanford Sleepiness Scale (SSS) |
| Karolinska Sleepiness Scale (KSS) |
| Visual Analogue Scale (VAS) of alertness/sleepiness |
| *Dozing behavior* |
| Epworth Sleepiness Scale (ESS) |
| Sleep-Wake Activity Inventory (SWAI) |

ings are made.[8] Within the conceptual framework described above, the sleep latency for each nap is a measure of the subject's ISP at the time. When the circumstances of the test are kept as constant as possible, the ISPs of the same subject measured at different times on the same day are moderately correlated, *e.g.*, $r = 0.61$, $n = 258$, $p < 0.001$.[10] However, Bonnet and Arand[11] have shown that the subject's activity during the few minutes before each nap, such as minor exertion at the bedside, can have a marked effect on the subsequent sleep latency. There is a carry-over effect on the subject's ISP for several minutes from one activity to another. The mean of the sleep latencies measured on the same day in the standardized MSLT gives a measure of the subject's SSP for that test situation, the MSLT-SSP. The test-retest reliability of the MSLT-SSP is quite high over periods of days to weeks: the mean correlation coefficient derived from five published series is 0.74 (range, 0.65-0.97). The figure usually quoted ($r = 0.97$) is an extreme value involving only 14 subjects, which has never been replicated.[12] The overall mean sleep latency in the MSLT for normal subjects is 11.5 ± 5.1 (SD) minutes. However, the reference range is more accurately defined by the 2.5 and 97.5 percentiles, and is 3.2-20.0 minutes.[9] The sensitivity and specificity of the MSLT in distinguishing the sleepiness of narcoleptics, who by definition have chronic EDS, from normal subjects, who do not, is the best way to measure the accuracy of the test. Using a cut-off value of  3 minutes for the MSLT, its sensitivity is only 52%, but its specificity is 98.3%. If a cut-off value of < 5 is accepted, the sensitivity would be 80.9% and the specificity 89.8%. Whatever cut-off values are adopted, the MSLT is less sensitive and specific than either the Maintenance of Wakeful-

ness Test (MWT) or the Epworth Sleepiness Scale (ESS) (see below). These results are not compatible with the 'rule of thumb' which, until recently, was the only method available for interpreting MSLT results.[13] It states that normal subjects have mean sleep latencies of between ten and 20 minutes. Those with a sleep latency of less than five minutes have 'pathological sleepiness', and those with between five and ten minutes are in a 'diagnostic gray area'. This 'rule' should be abandoned as it is very misleading. In the light of such evidence, it is difficult to maintain the MSLT as a gold standard, but this is still a matter of contention.[14]

One problem with the MSLT lies in its basic premise that the quicker we fall asleep when lying down in bed, the sleepier we must be. It appears that this is only partly true. Some normal subjects fall asleep in less than three minutes during the MSLT (in the range said to involve a 'pathological sleepiness') without any evidence of EDS in daily life.[15] Therefore, it has been suggested that the MSLT measures 'sleepability' rather than sleepiness.[16] Another explanation for this characteristic of the MSLT is that it only measures one SSP. For each individual subject, this involves a subject x situation-specific interaction, partly learned, which influences how that subject will respond to the particular test-situation, in this case, lying down during the MSLT. Some normal subjects who do not have EDS learn to fall asleep quickly after lying down in circumstances that may keep other subjects awake. This response is not easily predicted. It is simply an unwarranted assumption that, by extrapolation, the mean sleep latency in the MSLT gives an accurate measure of the subject's more general characteristic, his ASP in daily life. It is this latter that we usually want to measure. Johns[5,6] has presented evidence that different SSPs measured in the same subject, but under different circumstances, at about the same time, are only moderately correlated (Spearman's rho = 0.33-0.57). This is true whether the SSPs are measured subjectively or objectively (see below). This problem potentially exists for any test of sleepiness based on one SSP.

Within the conceptual framework proposed by Johns,[1,6] the MSLT-SSP should be seen as a reasonably reliable, but only moderately accurate, measure of the subject's ASP. The MSLT is more suitable for measuring changes in the sleepiness of the same subjects with time, as with the effects of drugs. It has the great advantage of being an objective test, but it is expensive and time-consuming. Despite endorsement by the relevant US authority,[17] it appears that few sleep centers routinely use the MSLT to quantify their patients' sleepiness. Nonetheless, it remains an important diagnostic aid for narcolepsy by demonstrating the occurrence of REM-sleep during daytime naps.[18]

*Maintenance of Wakefulness Test*

Another widely used test in this category is the MWT.[19] It is similar to the MSLT except that the subject sits in bed propped up on pillows, and tries to stay awake rather than fall asleep. The MWT measures the same variable as

the MSLT, the mean of sleep latencies during several naps, but in a different situation. Consequently, the two tests measure different SSPs and, as expected, their results are significantly, but not highly, correlated, *e.g.*, $r = 0.41$, $n = 258$, $p < 0.001$.[10] The mean of normal MWT-sleep latencies is 18.7 ± 2.6 (SD) minutes.[20] The reference range, defined by the 2.5 and 97.5 percentiles, is 12-20 minutes, and the MWT has a sensitivity of 84.3% and a specificity of 98.3%, with a cut-off value of < 12.[9] These results refer to the 20-minute version of the MWT. There is another version in which the subjects are allowed up to 40 minutes to fall asleep. The majority of subjects take longer to fall asleep during the MWT than during the MSLT, *i.e.*, the somnificity of the MSLT situation is higher than that of the MWT. However, some subjects repeatedly fall asleep more quickly when trying to stay awake than when trying to fall asleep.[10] This is an example of the subject x situation-specific interactions that provide an unpredictable source of variance in measurements of sleepiness in individual subjects (see below). The MWT shares with the MSLT its advantage of objectivity and its disadvantage of high cost. The MWT appears to be more useful than the MSLT for distinguishing changes in sleepiness as a result of therapeutic interventions, be that with nasal CPAP for OSA or stimulant drugs for narcolepsy.[10,21] It is the preferred objective test of sleepiness in the sense of one SSP. We simply do not have a gold standard test for the measurement of ASP.

*Other objective tests of sleepiness*

Several other objective tests of sleepiness rely on detection of the drowsy state at a particular time. Drowsiness is the fluctuating transitional state between wakefulness and sleep. Some physiological concomitants of the drowsy state, such as slow rolling eye movements recorded from the electro-oculogram,[22] spontaneous fluctuations in size of the pupil,[23] or changes in the frequency and amplitude of the EEG,[24] are objective and specific. If the requirement is to monitor a subject's ISP accurately over limited periods of time, from several hours to a few days (*e.g.*, while driving a truck or a train), then the continuous monitoring of some such physiological variable may be essential. One promising method uses video camera images of the subject's face and eyes (*e.g.*, of a truck or bus driver) to indicate the presence of the drowsy state from the pattern of eyelid movements and eye closures.[25,26] None of these methods has yet been standardized to form the basis of a clinically useful objective test of sleepiness, whether in the sense of continuous measurements of ISP, with indications of when a critical ISP has been reached, or a more limited test of a SSP in the laboratory.

Bennett *et al*.[27] have described a behavioral test of sleepiness, the Osler test, in which subjects indicate whenever they see a small light come on in front of them, as it does automatically for one second every three seconds. The subjects are said to be asleep after they have failed to respond to seven consecutive lights, when the test ends. The advantage of the Osler test over the MWT is

said to be the objectivity of its automatic scoring and the need for less equipment. Nevertheless, the Osler test takes all day, as do the MSLT and the MWT. It does not yet have a reference range of normal values, and its role is yet to be determined.

A variety of different driving simulator tests has been devised to address the problem of drowsy driving. All such tests are based on the premise that we can accurately predict a driver's sleepiness while driving, on the basis of measurements of his sleepiness at other times and in different circumstances. This premise is of doubtful validity (see below). Some tests such as Steer Clear are little more than simple reaction time tests.[28] Other tests use driving simulators that incorporate tracking and divided attention tasks that simulate actual driving more exactly. Such a test can readily distinguish the higher levels of sleepiness in groups of patients with OSA compared to normals. However, differences between individual subjects are much less clear-cut.[29] Many patients with OSA and EDS, by other criteria, perform normally in such tests. As yet, there is no standardized test of sleepiness that, by itself, can be used to withhold a driving license. However, if a subject's clinical history and safety record suggested a problem of EDS while driving, the diagnosis of a sleep disorder should be sought by overnight polysomnography, and some laboratory testing of sleepiness would be advantageous.

## Subjective tests of sleepiness

Some other tests of sleepiness rely on introspection and self-reports of feelings and symptoms that appear and change with drowsiness. Such subjective reports have formed the basis of several scales for measuring a subject's ISP. They are said to measure 'subjective sleepiness' as opposed to 'objective sleepiness' or sleep propensity. The Stanford Sleepiness Scale (SSS) is one such scale that is commonly used.[30] However, the SSS is not a unitary scale. Factor analysis of its item-scores reveals two factors, one apparently reflecting ISP, the other related more to fatigue, which is a disadvantage.[31] Scores on the SSS are not closely related to objective measurements of ISP made a few minutes later during the MSLT.[32] This should not surprise us because someone's ISP can change in a matter of seconds and because self-reports of feelings may not be very reliable, particularly for comparisons between subjects. The KSS is another method for measuring ISP.[22] So, too, is a visual analogue scale on which the respondent places a mark between two extremes of alertness and drowsiness to represent his ISP at the time. Scores on these tests have not been standardized.

A different kind of subjective test of sleepiness has been developed, the first and most commonly used of which is the ESS.[33] This depends on the subject's retrospective reports of dozing behavior in different situations. The ESS is based on the common experience that, if we doze off while sitting with our

head unsupported, the neck muscles that hold our head erect when we are awake relax, and this allows our head to drop forward. This nodding movement often rouses us briefly and makes us aware of having just dozed off and of our eyes having been closed, without necessarily being aware of the preceding drowsy state. The ESS is a simple self-administered questionnaire that asks the subject to rate on a scale of 0 to 3 his usual chances of dozing off in eight different situations that are commonly met in daily life. These situations are graded according to their somnificity. The item-scores give estimates of eight different SSPs. Each SSP is reasonably reliable in a test-retest sense over a period of months, *e.g.*, $r = 0.56$, $n = 87$, $p < 0.001$.[34] The ESS is the sum of the eight item-scores and can vary from zero to 24. It represents the subject's ASP across the eight situations in daily life. It does not to measure 'subjective sleepiness' because it does not assess feelings. That the ESS refers to observable behavior rather than subjective feelings is supported by the high correlation between the patients' and their partners' independent reports of the patients' dozing behavior (*e.g.*, rho = 0.74, $n = 50$, $p < 0.001$).[5] Rather, it measures the subject's sleep propensity subjectively in relation to a variety of particular situations. It is the only method that recognizes and addresses the requirement for measuring ASP. It is not a subjective equivalent of the MSLT or the MWT, each of which only measures one particular SSP.

Normal subjects in Australia have a mean ESS score of $4.6 \pm 2.8$ (SD),[35] and in the UK, $4.5 \pm 3.3$.[36] Based on the Australian sample ($n = 72$) and the 2.5 and 97.5 percentiles, the reference range of normal values is 0-10. The ESS has a high sensitivity (93.5%) and specificity (100%) in distinguishing narcoleptics from normal subjects. This has been independently confirmed in the UK, where the sensitivity was 97% and the specificity 100%.[36] Despite its reliance on retrospective subjective reports, the ESS has a high test-retest reliability, as high as the MSLT ($r = 0.81$ versus 0.74), and has very good evidence for its validity, accuracy, internal consistency, and unitary structure.[9,34] The ESS has been translated into many languages besides English, some translations being standardized, others not. To answer the ESS, the subject must have had recent experience of most of or all the situations described in its items. This has proved to be impossible in the case of some patients suffering from severe medical illnesses.[37] ESS scores do not vary consistently with age or gender.[35] However, evidence from Brazil suggests that there may be some ethnic or cultural differences.[38] The ESS costs very little and is easy to administer compared to the MSLT or MWT. Nevertheless, the fact that the ESS is based on subjective reports, with at least the potential for falsification and error, means that it cannot be a gold standard. For that we need an objective test to make the same measurements as the ESS makes subjectively. There is no such test at present. Any test of sleepiness should be used with a clear understanding of its limitations.

**Relationships between the results of different tests of sleepiness**

The relationship between the results of the MSLT and the ESS in the same subjects is a matter of contention, particularly for those researchers who have reported the lack of a significant relationship.[14] However, of all the 12 published series with correlations available at the time of writing, ten reported significant correlations ($p < 0.05$-$0.001$) with a mean $r = -0.36$ (range, -0.23 to -0.61). In five of these ten series, the number of subjects exceeded 100 and the largest series involved 522 subjects ($r = -0.29$, $p < 0.001$).[39] Thus, it cannot be said that we have insufficient data. It is clear that the relationship between the MSLT and the ESS is usually statistically significant, but it is not a close one. Nor is the relationship between the MWT and the ESS much closer; of three correlations published so far, the mean $r$ was -0.42 (range, -0.29 to -0.48), all being statistically significant (*e.g.*, Sangal *et al.*[10]). This is consistent with other evidence about the limited relationships between different SSPs, based on item-scores in the ESS.[5,6] In 987 Australian subjects (patients with sleep disorders as well as normal subjects), the mean of 28 Spearman correlation coefficients between their eight ESS item-scores was rho = 0.49 (range, 0.33-0.57). All these were statistically significant ($p < 0.0001$), but none was a very close relationship.[6] Even when different SSPs are measured objectively by the MSLT and the MWT, they are not more closely correlated than the SSPs measured by ESS item-scores. The results of recent experiments by Bonnet and Arand[11] are very relevant to this. They measured SSPs objectively in five different test situations, including the MSLT. The mean of four Pearson correlation coefficients between the results of the MSLT and the other tests was 0.53. With $n = 14$, only two of those correlations were statistically significant.

The disparity between the results of the MSLT and the MWT has led some researchers to believe that the MSLT measures the 'ability to fall asleep', whereas the MWT measures the 'ability to stay awake'.[10] While at face value this is so, it implies that the two 'abilities' represent two different generalized characteristics of each subject. Johns[5,6] argues differently, claiming that the MSLT and the MWT measure two different SSPs that, in part, relate specifically to each test situation, and are not generalized 'abilities'. If they were, there would be as many generalized 'abilities' as there are different situations in which to measure SSPs. He explains the relationship between any two SSPs in the same subject in terms of three different factors or sources of variance. The first relates to the subject's general level of sleepiness, his ASP. The second relates to differences in the somnificity of different postures, activities, and situations that are highly predictable for groups of subjects, less so for individuals. The third relates to subject x situation-specific interactions due to differences in the usual reaction of each subject to each test situation. It is such interactions that prevent patients suffering from psychophysiological insomnia from falling asleep in bed at night when, in a different cognitive setting, they can readily fall asleep in a chair, watching TV in the evening. Similarly, such patients can

sleep better than average on the first night in the sleep laboratory, when many others sleep worse than at home because of the first night effect. In 'normal' circumstances, most people fall asleep more quickly after lying in bed and preparing for sleep at night than they do when sitting and watching TV, *i.e.*, the somnificity of the former situation is usually higher than the latter. However, the 'unusual' responses of some subjects can increase, decrease, or reverse the effects of somnificity in some situations, but not in others.

The evidence to date suggests a tentative conclusion: we cannot rely on one particular SSP as an accurate predictor of a different SSP in the same subject, whether the SSPs are measured objectively by the MSLT or the MWT, subjectively by the ESS, or by any other means. Two different SSPs in the same subjects will often be moderately correlated, but sometimes not. The same will be true for predictions of a subject's ISP at a particular time. If this conclusion is accepted, it has important ramifications; for example, with the assessment of a driver's ISP at a particular time, based on a measurement of his ISP or an SSP when he is not driving. Much more research is needed on this topic. However, a corollary of this conclusion is that a measurement of a subject's general level of sleepiness in his daily life (his ASP) is likely to be more accurate if it is based on a variety of different SSPs rather than on one. This could explain the documented accuracy of ESS as a measure of ASP, despite its perceived inaccuracy because it is based on subjective reports.

## Sleepiness in patients with obstructive sleep apnea/snoring

The assessment of sleepiness in individual patients is complicated. So, too, is the assessment of the severity of OSA. However, one thing is clear – groups of patients with OSA have higher levels of sleepiness than do groups of normal subjects.[21,27,40] It has generally been assumed that the repeated fragmentation of sleep by respiratory arousals, combined with repeated episodes of arterial oxygen desaturation, causes the EDS. Certainly, when the OSA is successfully treated by nasal CPAP, the levels of sleepiness in groups of patients are invariably reduced when assessed by the ESS,[41,42] less reliably so by the MWT, and least reliably by the MSLT.[10] However, the levels of sleepiness in treated patients often remain in the upper half of the normal range for reasons that are not clear. The frequency of apneas and hypopneas per hour of sleep (the apnea-hypopnea index, or AHI, otherwise known as the respiratory disturbance index, or RDI) is commonly used as the main measure of the severity of OSA. Another measure is the lowest level of arterial oxygen saturation reached during apneas and hypopneas overnight (minimum $SaO_2$). There have been many attempts to correlate the RDI and minimum $SaO_2$ with patients' sleepiness, whether assessed by the MSLT, MWT, or ESS. None of the correlations has been high. Some have been statistically significant,[21,40] but many have not.[43] For some time, it was thought that a much better index of the severity of OSA

would be the respiratory arousal index, separating those apneas and hypopneas that caused arousal. This has not been found to be the case, even when subcortical arousals and a sensitive index of respiratory effort were included.[3] The mechanisms by which EDS is caused in OSA remain uncertain.

Some patients who snore persistently without having OSA (*i.e.*, RDI < 5/hour) have levels of sleepiness significantly higher than normal subjects, but lower than many patients with OSA.[35,40] The mechanism for this is also uncertain. There is no measure of EDS that can be used alone to quantify the severity of OSA in individual patients. Sleepiness should be used as one measure among many others, such as body mass index, that describe a patient's clinical condition. There are occasional patients with severe OSA (RDI > 50/hour) with frequent episodes of arterial oxygen desaturation who do not have EDS, clinically or by ESS scores, etc. There is no evidence that this arises simply from the inaccuracy of our measurements of sleepiness. There may be several reasons why EDS and OSA are not closely related in individual subjects, as others have described.[3,43] One reason is that much of the variance in measurements of sleepiness between subjects is due to factors other than sleep disorders, as is now recognized. Another reason may be that there are sleep disorders other than OSA, such as restless legs syndrome and periodic limb movement disorder, which are common disorders that often occur with OSA and contribute to EDS, but which are under-diagnosed.

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# HIGHLIGHTS ON DIAGNOSIS

# SOMNOSCOPY

## A technique for analysis and postsurgical follow-up in snoring and obstructive sleep apnea syndrome patients

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### Introduction

Somnoscopy is a new technique to evaluate, under direct visualization and during sleep, the pharyngolarynx and esophagus in snoring patients or patients with suspected obstructive sleep apnea syndrome (OSAS). With this technique, we are able to evaluate the different locations and degrees of pharyngeal and laryngeal obstruction in different positions (back, side). At the same time, a gastroesophageal reflux problem can be assessed.

### Technique

The exploration is performed at the bedside, without using any medication. While drinking clear water, a flexible fibroscope (Storz, diameter 3.5 mm, length 75 cm) is introduced through the nose and placed in the esophagus at the level of the lower esophageal sphincter (LES). During sleep, the fibroscope is pulled stepwise backwards to the lower border of the upper esophageal sphincter (UES), the retrocricoid area, the border of the epiglottis, the palatal arch, and the rhinopharynx. Simultaneously, a polysomnography and, if necessary, pH-metry is performed. The findings are registered on a S-VHS videotape for subsequent comparison or assessment.

### Observations

During pre-somnoscopic exploration in the office, obstructions in the upper airway are visible at different levels: in the nose (septum deviation, hyperplas-

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tic turbinates, polyposis etc.), in the rhinopharynx (adenoids, hyperplastic dorsal part of the turbinates), and in the pharyngeal region (hypertrophic pharyngeal tonsils, hypertrophic soft palate and uvula, large tongue base or hypertrophic tongue tonsils).

During somnoscopy, other and different types of obstructions are observed in different patients, at the level of the palatal region, such as: a side-to-side closure; an antero-posterior closure; or a circular closure.

Also, lower in the oropharyngeal region, during somnoscopy from the oral cavity, we can see that the body of the tongue falls backwards in supination, reducing or closing the pharyngeal and/or oral airway. The dorsal pharyngeal wall changes its shape. Muscle relaxation results in an angled pharynx; the muscles prolapse partially into the pharyngeal lumen. The raphe rests in its place. Very often, especially in older people, the lateral pharyngeal walls become floppy. During inspiration, the negative pressure sucks the lateral walls to the midline and produces pharyngeal flutter with functional narrowing of the pharyngeal airway or pharyngeal collapse. Aspiration of the epiglottis to the laryngeal entrance can be seen during inspiration.

During somnoscopy, redundant aryepiglottic folds and/or postcricoid and arytenoid edema are observed. These are consequences of an airway obstruction, which is located above the structures mentioned.

## Discussion

OSAS patients are usually evaluated by fiberoptic endoscopy when they are awake. Some groups perform endoscopy using sedatives or hypnotics.[1,2] Our results have demonstrated that, during sleep, potential sites of upper airway compromise are difficult to predict, with a wide variability between patients. Therefore, it is better to perform endoscopy while the patient is asleep in order to establish the pattern and location of the obstruction. In order to exclude functional alterations due to medication, somnoscopy is carried out in the horizontal position *without any medication* while the patient is asleep. This allows polysomnography to be performed simultaneously, with minimal discomfort to the patient.

Obstructions in the upper airway produce negative pressure during inspiration in the part of the airway that is located below.[3,4] In heavy snorers or OSAS patients, continuous negative pressure (suction), with continuous inspiratory efforts, result in an enlarged pharyngeal mucosa, including a large edematous uvula, a long and hypertrophic soft palate and redundant pharyngeal mucosa.[5] This obstruction in the upper airway leads to significant changes in the esophageal pressure, which explain the opening of the esophagus lumen and, in cases of weak LES or sliding hernia, the opening of the cardia with reflux.[6] If this is the case, reflux to the esophagus is supported by the horizontal position during sleep.[7]

A close relationship has been established between gastroesophageal reflux disease (GERD) and some obstructive problems combined with respiratory difficulties.[8,9] Reflex connections between the digestive tract and respiratory system have been reported.[10] It is well known that acid reflux via the pharynx to the upper airway is an important factor for developing asthma.[11] Ciliary mucosa is very sensitive to acid reflux and is easily damaged by it. Important factors for reflux to the pharynx are: the negative pressure of the pharynx sucking the reflux out of the UES, and the significant decrease of spontaneous swallowing during sleep. The deglutition which prevents the reflux of gastric juice via diffusion, and eliminates contact with the pharyngolaryngeal structures, is almost absent.[12]

In patients with GERD, different pathological changes of the laryngeal mucosa are found, which result in narrowing of the upper airway, including posterior laryngitis, hypertrophic interarytenoid tissue, edematous vocal cords, diffuse supraglottic edema, vocal cord granulomas, and subglottic inflammation.[13]

These are important reasons for assessing concomitant GERD in patients with OSAS. Therefore, during somnoscopy, the fibroscope is placed near the LES and below the UES in order to establish the presence of gastroesphageal reflux.[14] If necessary, pH-metry is performed.

## Conclusions

At the present time, the different surgical techniques for OSAS are far from satisfactory for either the patient or the doctor. Based on our experience, treatment should be strongly individualized. Somnoscopy is probably the most precise technique for defining upper airway characteristics in patients with OSAS; when performed simultaneously with polysomnography, it provides the ENT surgeon with a new possibility for precise diagnosis and post-therapeutical follow-up; it guarantees quality control and results in better cost-effectiveness.

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# AN ABBREVIATED METHOD FOR ASSESSING UPPER AIRWAY FUNCTION IN OBSTRUCTIVE SLEEP APNEA

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## Introduction

Previous studies have demonstrated that upper airway collapsibility varies widely over the spectrum from health to disease, and that increases in upper airway collapsibility play a central role in the pathogenesis of obstructive sleep apnea.[1] Measurement of pressure-flow relationships in the upper airway was used to define upper airway collapsibility as the level of nasal pressure below which the upper airway closed (critical closing pressure, $P_{crit}$) and the upstream resistance ($R_N$) as the inverse of the slope of the pressure-flow relationship.[2]

Previous studies utilized a lengthy protocol to establish a pressure-flow relationship from multiple measurements of tidal airflow taken over a wide range of nasal pressures during prolonged periods of stable sleep. This method does not allow $P_{crit}$ and $R_N$ to be determined repeatedly under various test conditions within a single night. Therefore, we developed an abbreviated method for generating upper airway pressure-flow relationships from multiple breaths during sleep.

## Methods

We determined pressure-flow relationships in the upper airway, as described earlier.[2] Briefly, the patient sleeps with a nasal mask connected to a positive and negative pressure source. Nasal pressure is lowered repeatedly during consecutive breaths until maximal inspiratory airflow ($V_I$max) falls to zero.

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Following step decreases in nasal pressure during non-rapid eye movement (NREM) sleep, we observed significant alterations in $V_I$max within the six ensuing breaths for supine ($F = 11.5$, $df = 5$, $p < 0.001$) and side ($F = 9.9$, $df = 5$, $p < 0.001$) positions. Our findings indicate that $V_I$max fell to a quasi-steady state level for the third through fifth breath after step decreases in nasal pressure. We then constructed $V_I$max versus $P_N$ relationships from data obtained for the supine and side positions, and calculated the $P_{crit}$, $R_N$ and confidence intervals around these parameters.

## Results

This protocol was applied to a group of ten middle-aged obese men, with polysomnographic evidence of severe obstructive sleep apnea (NREM respiratory disturbance index 61.7 (7.0) episodes/hour). When comparing $P_{crit}$ in the supine and side positions, we found that it fell from 1.8 (CI 1.5) to –1.1 (2.6) $cmH_2O$ ($p = 0.009$) in NREM sleep (Fig. 1). This resulted in a mean fall in $P_{crit}$ of 2.9 (2.0) $cmH_2O$ in the side position. In contrast to the positional responses in $P_{crit}$, no significant difference in $R_N$ was detected with positional maneuvers.

## Discussion

We developed an abbreviated, standardized method for characterizing upper airway function during sleep, by examining pressure-flow relationships in the

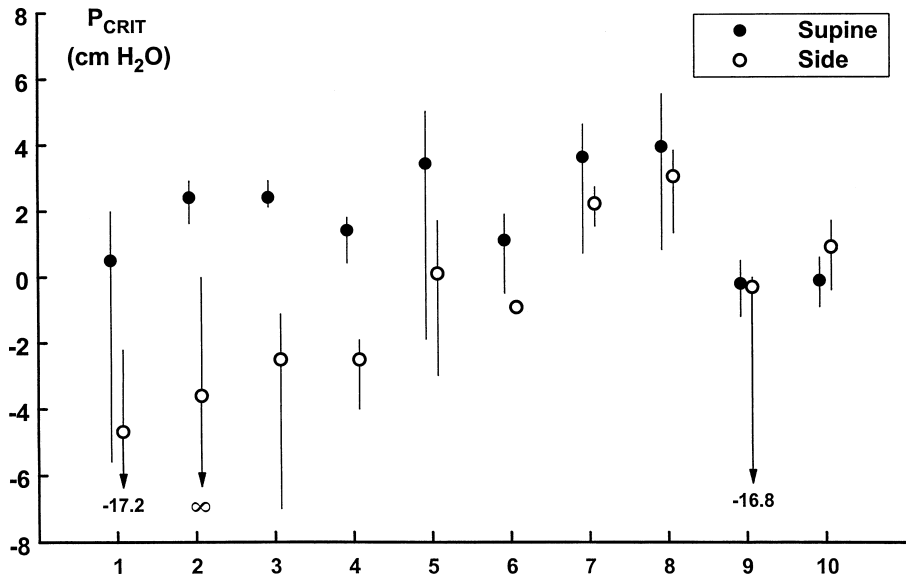


*Fig. 1.* The critical pressure is illustrated for each patient in the supine and side positions in NREM sleep ($n = 10$, $p = 0.009$).

upper airway in patients with obstructive sleep apnea. These relationships were constructed from breaths obtained after lowering nasal pressure abruptly from a relatively high 'holding' pressure level. When several breaths were evaluated after step reductions in nasal pressure, we found that the level of maximal inspiratory airflow fell to a relatively low level within the first three breaths, and remained stable at this level through the fifth breath.

Having demonstrated a quasi-steady state response in airflow for breaths three through five after an abrupt reduction of nasal pressure, we then utilized these breaths to construct pressure-flow relationships for NREM sleep in the supine and side positions. From these relationships, we characterized two parameters of upper airway function – the pharyngeal critical pressure ($P_{crit}$) and the resistance upstream to the site of pharyngeal collapse ($R_N$) – both of which determine the severity of airflow obstruction during sleep.

By repeated measurement of these parameters, our method allowed us to distinguish small decreases in $P_{crit}$ as patients moved from the supine to the side position. This finding with regard to changes in position is consistent with previous studies[3,4] demonstrating a similar direction and magnitude of changes in critical pressure. When confidence intervals did not overlap, we took this to indicate that the critical pressure decreased significantly in the side position. Thus, our methods have helped to establish the precise mechanism for relief of upper airway obstruction ($P_{crit}$ versus $R_N$) in patients with OSA, as well as the impact of positional changes on the severity of upper airway obstruction in individual patients. In further studies, our methods may help in the investigation of clinical and physiological factors influencing the severity of upper airway obstruction during sleep, and may serve as a guide to clinicians in their selection of therapy for these patients.[5]

## Acknowledgments

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# ALLERGOMETRIC SCREENING IN OBSTRUCTIVE SLEEP APNEA SYNDROME PATIENTS

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## Abstract

A skin prick test (SPT) for the most common inhalants was performed in 40 adults and 59 children affected by snoring and, in some cases, by associated apnea, in order to verify whether the incidence of atopy in patients affected by obstructive sleep apnea syndrome (OSAS) or snoring is higher than in normal subjects. Adult patients were selected on the basis of clinical history and of pulsoximetry monitoring performed during sleep at home; diagnosis was then confirmed by polysomnography. Children were also selected on the basis of clinical history and lymphatic hypertrophy of the tonsillar structures was confirmed by fibroscopy or radiographical examination. SPT positivity was observed in 40% of adult patients and in 54% of children. Such percentages were far higher than those reported in the normal population by other authors. It is concluded that, as one of the most important causes of upper airway obstruction, allergy can play a major role in snoring and in OSAS pathogenesis, and should be routinely looked for during the evaluation of these patients.

## Introduction

Nasal obstruction plays a major role in snoring pathogenesis and can contribute to the obstructive sleep apnea syndrome (OSAS),[1,2] OSAS is characterized by inspiratory collapse of the upper airways during sleep; this collapse originating from high negative pressure in the pharynx that exceeds the muscular tone of the pharynx walls.[3-5] Nasal obstruction can contribute to negative pressure by increasing the resistance to air flow. Moreover, in usual snoring patients breathing through the mouth while asleep, the soft structures of the upper airways are directly exposed to the atmospheric pressure.

Allergic rhinitis or specific nasal hyperactivity (SNH) is one of the commonest causes of nasal obstruction, having an incidence of around 20% in the general population.[1,6] Nasal congestion originating from SNH causes a significant decrease of air flow through the nose and, consequently, can interrupt the sleep circle, decrease attention, and induce diurnal drowsiness.[7-10] Some studies have

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pointed out that increased nasal resistance can cause nocturnal apnea, hypopnea, or snoring.[11-13] On the other hand, Duchna *et al.* registered a positive skin prick test (SPT) in 49% of patients affected by OSAS.[14]

In children, a higher risk of developing OSAS is associated with craniofacial malformations, neuromuscular dystrophy, and adenotonsillar hypertrophy.[15-17] Allergy can contribute to upper airway chronic obstruction by hypertrophy of the adenotonsillar lymphatic tissue. In children affected by OSAS, both snoring and drowsiness are less pronounced compared to adults. On the contrary, the usual nocturnal hyperactivity observed is characterized by excitement, nightmares, and enuresis. Stagnating secretion and lymphatic phlogosis can cause serious rhinopharyngeal obstruction, and the subsequent breathing pauses make the sleeping child very agitated (*pavor nocturnus*). In children affected by OSAS, allergic disease occurs three times more frequently (about 36%) than in the general pediatric population.[18-21] The purpose of this study was to investigate the incidence of atopy to the most common inhalants in patients affected by OSAS.

## Material and methods

### *Patient selection*

After obtaining institutional approval and informed consent, 40 adult patients (37 males and three females, aged 34-65 years) and 59 children (29 males and 30 females, aged 3-13 years), affected by snoring or nocturnal sleep apnea, were enrolled in the study. Diagnosis was based on medical history, general physical examination, ENT examination, and nasal fibroscopy.

### *Patient evaluation*

In children, X-rays were usually associated with fibroscopy to evaluate the size of the adenoids.

In adults, domiciliary pulsoximetry was performed while the patients were asleep. If oxyhemoglobin saturation fell below 90% for more than ten minutes, or if it fell below 75%, polysomnography was also carried out to confirm the diagnosis of OSAS, during which tidal volume, nasal and oral air flow, cardiac rhythm and frequency, position of the body, and snoring sounds were registered. The apnea-hypopnea index (AHI) and LSAT index (the lowest value of hemoglobulin saturation observed during polysomnography) were also determined. Polysomnography was regarded as positive when AHI was over 15 events per hour.

The OSAS patients were divided into four classes of increasing gravity, according to Simmond:

I. mild (AHI: 30 events per hour; LSAT: 85%)

II. moderate (AHI: 30 events per hour; LSAT: 84-75%)
III. moderate-severe (AHI: 30 events per hour; LSAT: 74-51%)
IV. severe (AHI: 60 events per hour; LSAT: 51%)

*Allergometric screening*

Allergometric screening was performed by SPT for the most common inhalants: *Dermatophagoides pteronyssimus* (DPt), *Dermatophagoides farinae* (DF), grass pollen, pellitory, *Asteracee*, *Miceti*.

Allergens were tested on the forearm surface, at a distance of about 5 cm from each other. SPT positivity was divided into four degrees of positivity:

1. mild hyperemia
2. hyperemia with mild edema
3. a round area of edema and hyperemia, the diameter of which being over 1 cm
4. the presence of hyperemic *pseudopodi*

Tests with saline and histamine were also performed as a control.

## Results

*Adults*

Sixteen out of 40 adult patients (40%) had a positive SPT (Fig. 1). The allergens that were most commonly positive at SPT were the dermatophagoides (12 patients with a positive SPT), grass pollen (ten patients) and parietaria (five patients) (Fig. 2).

Pulsoximetry was negative in four out of 16 atopic patients, who had not undergone polysomnography nor had shown any anatomical alteration on physical

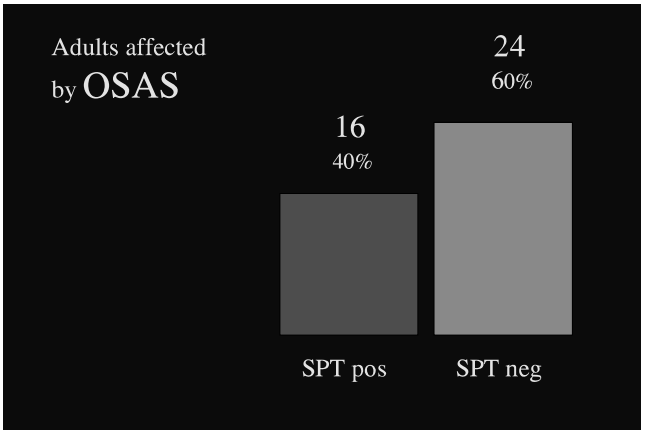


*Fig. 1.* SPT in adults.


*Fig. 2.* Type of allergy in adults with a positive SPT.

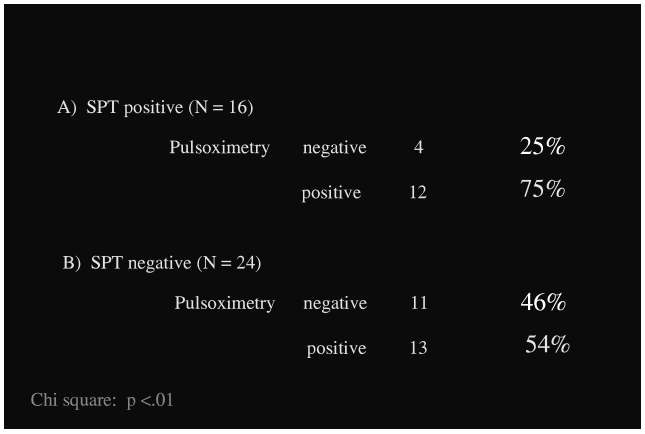


*Fig. 3.* Pulsoximetry in adults with a positive or negative SPT.


*Fig. 4.* Polysomnography in adults with a positive or negative SPT.

ENT examination. The other 12 atopic patients underwent polysomnography because of positive pulsoximetry (Fig. 3) and were classified as Simmond's class I (four cases), class II (two cases), class III (three cases), and class IV (three cases) (Fig. 4). The patients in classes I and II did not show any particular anatomical alteration at ENT physical examination, apart from hypertrophy of the nasal *turbinates* caused by SNH and, in two patients, deviation of the nasal septum; on the contrary, SPT was characterized by a marked positivity. The patients in classes III and IV showed more relevant findings on physical ENT examination. Hypertrophy of the uvula and posterior pillars, laxity of the soft palate, macroglossia, and tonsillar hypertrophy were observed, which were deemed to be directly involved in the OSAS pathogenesis and were evaluated for surgical treatment. Hypertrophy of the nasal *turbinates* was also observed, even though it was less prominent than the other alterations; furthermore, SPT only showed mild positivity in all class III and IV patients.

*Children*

Thirty-two of 59 children (54%) had a positive SPT (Fig. 5). The allergens that were most commonly positive on SPT in children were the dermatophagoides (16 cases), grass pollen (18 cases), and parietaria (eight cases) (Fig. 6). The only prominent finding on ENT examination was tonsillar hypertrophy, which was observed in 13 atopic children (41%) versus 12 non-atopic children (44%) (Fig. 7).

## Discussion and conclusions

In agreement with other reports in the literature,[14,17] this study shows that patients affected by snoring or by OSAS present with a higher incidence of SPT

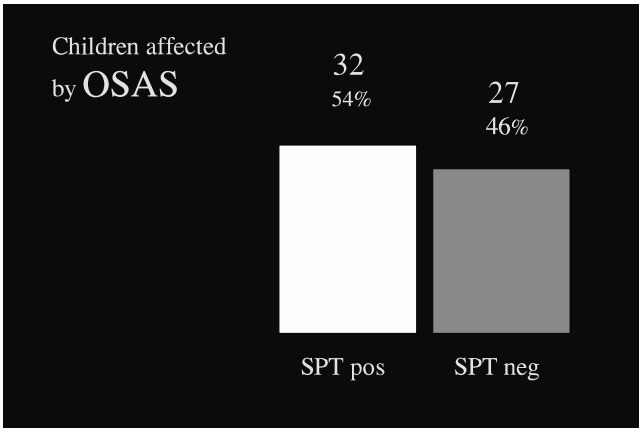


*Fig. 5.* SPT in children.

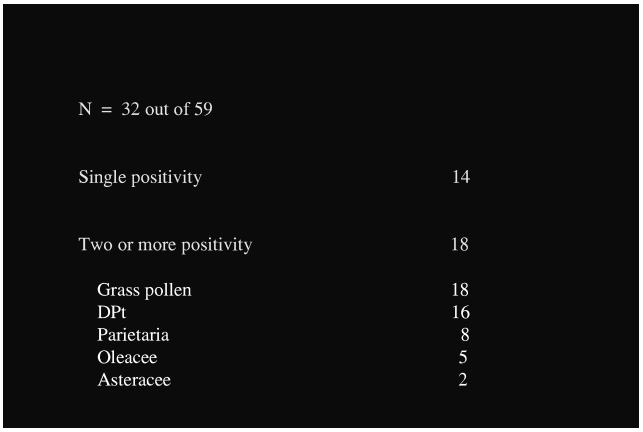


*Fig. 6.* Type of allergy in children with a positive SPT.

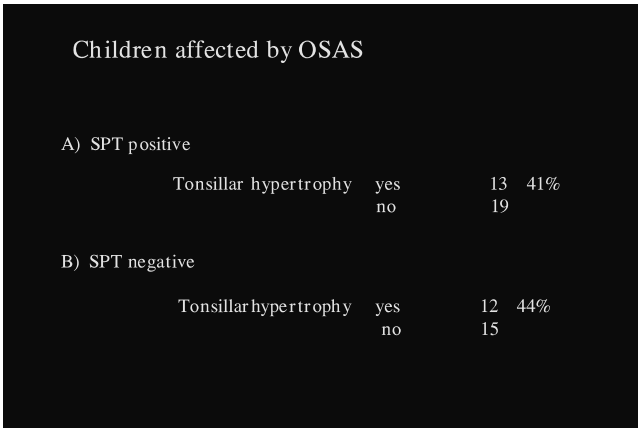


*Fig. 7.* SPT and tonsillar hypertrophy.

positivity (40% in adults and 54% in children) compared to the general population. These results also suggest that nasal obstruction, of which SNH is one of the most frequent causes, plays a major role in the pathogenesis of snoring and OSAS.

Since symptomatic and specific treatment of SNH could possibly improve snoring and OSAS, we suggest that atopy should be investigated in all patients affected by snoring or OSAS. To this purpose, blood tests including PRIST and RAST (to single inhalants selected on the basis of medical history) could improve the sensitivity of the diagnosis of atopy.

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# CEPHALOMETRIC AND ENDOSCOPIC FEATURES IN SNORERS AND PATIENTS WITH OBSTRUCTIVE SLEEP APNEA

## A multivariate analysis

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### Introduction

Obstructive sleep apnea (OSA) can be considered a potentially life-threatening disease, characterized by the recurrent collapse of the supralaryngeal airway during sleep. Unfortunately, the specific cause of the pharyngeal obstruction is still unknown, but in the last decade many studies have pointed out the importance of craniofacial and soft tissue abnormalities, such as severe retrognathia, macroglossia, redundant pillars, tonsillar hypertrophy, length of the soft palate, and crowded oropharynx, as being possible risk factors in the development of this obstruction.[1-2] Despite the large number of articles published on OSA, and with the exception of only the well-established body mass index (BMI), we have as yet been unable to find specific physical parameters to explain OSA.

There are many methods to examine the upper airway. In clinical practice, routine fiberoptic endoscopy and cephalometric radiography are probably the most useful methods for detecting the sites and degree of abnormality of the anatomical structures involved in the development of OSA. Pharyngoscopy allows direct observation of the dynamic appearance of the pharynx, and it is used to evaluate the physiological changes in the airway. However, nasopharyngoscopy only examines the lumen of the upper airway system and does not provide measurements of the surrounding soft tissue structures.[3] Cephalometric radiography is widely available, easy to perform, and less expensive than CT or MRI. The limitations of cephalometry are related to its two-dimensional representation of a three-dimensional structure, its inability to provide

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volumetric data, or to evaluate important upper airway soft tissue structures, such as the lateral pharyngeal walls or parapharyngeal fat. Moreover, cephalometry provides limited information about anterior-posterior structures, no information about lateral structures, and it cannot be performed dynamically during the sleep.

The aim of this study was to evaluate, in a large population of snorers with or without OSA, the relationship between anthropometric (BMI, sex, age), endoscopic and cephalometric features, and the presence and severity of OSA.

## Material and methods

One hundred and eighty-two patients (154 males and 28 females) referred to us for habitual snoring and disturbed sleep were submitted to a clinical, endoscopic, cephalometric, and polysomnographic evaluation.

*Polysomnography:* the sleep studies were performed using a portable monitor (MESAM IV) to record the following variables simultaneously: nocturnal snoring sound, arterial oxygen saturation, ECG, body position. To determine the seriousness of sleep apnea, we considered the oxygen desaturation index (ODI), *i.e.*, the rate of oxygen desaturation over 4% per hour of sleep: patients with ODI <15 were classified as snorers; those with ODI ≥=15 as mild to severe apnoics (mild: ODI ranging from 15-29; moderate: ODI from 30-44; severe: ODI >45).

*Cephalometric radiographs:* lateral cephalometric radiographs were obtained using the technique described by Riley *et al.*[4] The following measurements were made from the radiograph: MP-H (position of the hyoid bone from the mandibular plane); PAS (posterior airway space); degree of maxillary (SNA) and mandibular development (SNB); length of the soft palate (PNSP); mandibular plane (MP).

*Fiberoptic endoscopy with Müller's maneuver:* performed by means of a flexible nasopharyngoscope passed transnasally to evaluate the upper airway lumen. Müller's maneuver was performed to determine the extent of retropalatal (Müller RP) or retrolingual (Müller RL) obstruction; it was considered significant when there was a collapse of more than 50%.

A stepwise logistic regression was used to determine which cephalometric and/or endoscopic variable correlated with ODI.

## Results

The mean age of the patients was 51.3 years (SD: 10.5), ranging from 32-72 years. BMI ranged from 20.7-53.2, with a mean of 28.8 (SD: 5.0); 48.9% of the patients had a BMI <28, 51.1% >28.

Average ODI was 26.52% (SD: 23.10), ranging from 0-105. Seventy-five patients (41.2%) were simple snorers, 40 (22%) were affected by mild OSA, 24 (13.2%) by moderate OSA, and 43 (23.6%) by severe OSA.

The results of the cephalometric analysis are reported in Table 1.

As far as endoscopic evaluation was concerned, a retropalatal obstruction was identified in 147 patients (80.8%) using Müller's maneuver; 55 of these patients (30.2%) also had a retrolingual obstruction. Twelve patients (6.5%) had retrolingual collapse only.

A stepwise logistic regression table was used to correlate cephalometric and endoscopic data with the presence of OSA (Table 2). A second stepwise logistic regression table was used to correlate cephalometric and endoscopic data with severe OSA (Table 3).

Finally, we analyzed the association of these factors (BMI >28, MP-H >18 mm, Müller RL+) in all the patients (Table 4).

## Discussion

It is well established that OSA is associated with a disproportionate anatomy of the upper airway. Many studies have assessed these abnormalities using various methods including fiberoptic endoscopy, cephalometry, CT, and fluo-

*Table 1.* Cephalometric results

| *Parameter* | *Mean* | *Cut-off* | *PTS>cut-off* | | *PTS<cut-off* | |
|---|---|---|---|---|---|---|
| SNA | 82.6 ± 5.6° | 84° | 66 | (36.3%) | 116 | (63.7%) |
| SNB | 80.5 ± 5.5° | 82° | 56 | (30.8%) | 126 | (69.2%) |
| PAS | 9.5 ± 3.7 mm | 11 | 41 | (22.5%) | 141 | (77.5%) |
| PNSP | 46.2 ± 7 mm | 39 | 162 | (89%) | 20 | (11%) |
| MP-H | 26 ± 3.7 mm | 18 | 158 | (86.8%) | 24 | (13.2%) |
| MP | 74.8 ± 6 mm | 76 | 67 | (36.8%) | 115 | (64.2%) |

*Table 2.* Dependent variable correlation ODI >15

| *Parameter* | *Coefficient/SE* | *p value* |
|---|---|---|
| BMI >28 | 3.693 | 0.0000 |
| Sex (M) | 3.629 | 0.0001 |
| MP-H >18 mm | 3.342 | 0.0002 |
| PNSP >39 mm | 2.263 | 0.0201 |
| SNB <82° | 1.912 | 0.0549 |
| Müller RL+ | 1.823 | 0.0636 |
| PAS >11 mm | 1.662 | 0.0967 |
| SNA <84° | - | NS |
| Age > 50 | - | NS |
| MP >76 mm | - | NS |
| Müller RP+ | - | NS |

*Table 3.* Dependent variable correlation ODI >45

| *Parameter* | *Coefficient/SE* | *p value* |
|---|---|---|
| BMI >28 | 2.721 | 0.0069 |
| Müller RL+ | 2.507 | 0.0119 |
| MP-H >18 mm | 1.697 | 0.0306 |
| Sex (M) | - | NS |
| SNB <82° | - | NS |
| PNSP >39 mm | - | NS |
| PAS >11 mm | - | NS |
| SNA <84° | - | NS |
| Age > 50 | - | NS |
| MP >76 mm | - | NS |
| Müller RP+ | - | NS |

*Table 4.* Association of risk factors

| *Association* | *Total* | *Snorers* | *Mild OSA* | *Moderate OSA* | *Severe OSA* |
|---|---|---|---|---|---|
| 3+(BMI, MP-H, Müller RL) | 37 | 5 | 8 | 6 | 18 |
| BMI+/MP-H+ | 47 | 12 | 14 | 7 | 14 |
| MP-H+/ML+ | 25 | 11 | 5 | 3 | 6 |
| BMI+/ML+ | 2 | 1 | - | - | 1 |
| BMI+ | 7 | 4 | 2 | 1 | - |
| MP-H+ | 49 | 28 | 11 | 6 | 4 |
| ML+ | 3 | 3 | - | - | - |
| 3–(BMI, MP-H, Müller RL) | 12 | 11 | - | 1 | - |
| Total | 182 | 75 | 40 | 24 | 43 |

roscopy.[5,6] Of these techniques, endoscopy combined with cephalometry is the best method currently available for otolaryngologists to evaluate a large number of patients with abnormalities of the soft and skeletal tissue, who have a high risk of OSA. Various reports suggest that CT provides more information, particularly on lateral structures, but this examination is carried out while the patient is awake, and therefore does not predict the occurrence of hypopharyngeal collapse during sleep.[7]

In our study, the cephalometric endoscopic and anthropometric features of 182 snoring patients, with or without OSA, were statistically assessed in order to determine specific characteristics predictive of the presence and severity of OSA. Multivariate analysis indicates that there is a significant correlation between different cephalometric variables (increased distance from the mandibular plane to the hyoid bone, increase in the length of the soft palate, posterior mandibular displacement), being male, high BMI, retrolingual collapse, and the presence of OSA. This is in agreement with the results of previous studies

which reported that OSA patients have more airway abnormalities than snorers.

Results of logistic regression also suggest that BMI, high MP-H, and the presence of remarkable retrolingual collapse, are the only significant and independent variables that correlate with the severity of OSA. Obesity has previously been reported as an important element provoking OSA.[8] In our analysis, hypopharyngeal displacement of the base of the tongue expressed by high MP-H measurement is the strongest anatomical risk factor for the development of OSA, independent of obesity. This result is in contrast to recent reports suggesting that the relationship between mandibular plane to hyoid distance and severity of OSA appear to be secondary to variation in neck circumference (obesity).[8,9] These results are in agreement with a recently published somnofluoroscopic study in which a significant correlation between hypopharyngeal collapse during sleep and measurements of MP-H with the patient awake and upright was reported.[7]

With regard to retrolingual collapse, although endoscopy is generally considered to be a limited predictor of OSA, because it depends on patient compliance and examiner assessment, this variable appears to be consistent with the presence of a lower position of the hyoid bone. This observation confirms the importance of the position of the hyoid: this serves as the central anchorage of the tongue muscles and therefore has a great impact on tongue stage and posture, affecting the patency of the hypopharynx. The vertical posture of the tongue during sleep also produces an increase in the length of the airway; this phenomenon contributes to the instability of the pharynx during sleep.

OSA appears to stem from multiple causes, one of which is the anatomical factor. In our analysis, risk factors were present in both groups, snorers and OSA patients, but were more significant and relevant in OSA patients. Further studies are necessary to outline other factors responsible (anatomical and functional) and the relationship between them.

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# SLEEP APNEA AND MORBIDITY*

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Several lines of evidence have shown that nightly (habitual) snoring and sleep apnea are related to cardiovascular morbidity and mortality. Contradictory reports have also been published. In a meta-analytic, evidence-based study of the literature, the relationship between obstructive sleep apnea and morbidity, as well as the effectiveness of the treatment of obstructive sleep apnea syndrome (OSAS) were reported to be questionable. The latter study omitted many important studies on sleep apnea. No experimental evidence on the effects of sleep-related breathing disorders on the cardiovascular system was discussed.

The authors discuss different epidemiological studies and provide various new results from our prospective study of snorers and controls, with more than 15 years of follow-up.

The differences in inferences can partly be explained by the differences in methodology. On the other hand, the recent study by Wright *et al.* also shows that well-conducted, randomized clinical trials are needed. CPAP is effective, but the long-term (three to five years at least) effectiveness of the surgical treatment of OSAS remains to be proved. Moreover, the effectiveness of the treatment of upper airway resistance syndrome (UARS) still has to be studied. In these trials, outcome parameters should include traditional indices as well as those of daytime sleepiness and quality-of-life issues.

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*Surgery for Snoring and Obstructive Sleep Apnea Syndrome, p. 321*
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# OBJECTIVE EVALUATION OF THE PHARYNGEAL AIRWAY IN SNORING AND OBSTRUCTIVE SLEEP APNEA PATIENTS USING ACOUSTIC REFLECTOMETRY*

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Pharyngeal size and the dynamic behavior of the pharynx are important factors in modulating pharyngeal airflow and, therefore, in the production of obstructive sleep apnea. Assessment of the upper airway should not only include the identification of the possible site(s) of obstruction, but also assessment of pharyngeal compliance. Changes in pharyngeal area in response to changes of the intraluminal pressure of the pharynx produced by lung volume changes have been employed for assessment of pharyngeal function, and reflect pharyngeal 'floppiness'. The acoustic reflectometry technique has the potential both to localize the site of obstruction and to test pharyngeal function. The aim of this work is to present a description of the normal curve, normal pharyngeal and glottic cross-section areas, and the results of testing the pharyngeal cross-section area in response to changes in pharyngeal intraluminal pressure in normal volunteers; and finally, to present examples of cases in which the acoustic reflectometry technique is useful in localizing the anatomical site of pharyngeal airway obstruction.

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# ADVANTAGES OF MEASURING AIRFLOW IN THE HYPO- AND EPIPHARYNX WITH INTERNAL THERMISTORS*

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Measurement of airflow in patients suffering from breathing disturbances during sleep is usually accomplished by an oro-nasal thermistor located at the upper lip. Detection of hypopneas using this system may be difficult because the external thermistor is very sensitive to airflow, but has difficulty in differentiating between high and low airflow.

The scoring of hypopneas has been reported to have relatively poor reproducibility between different observers. In order to ease diagnosing hypopneas and to measure flow in different locations in the upper airways, the authors introduced a new method using internal thermistors contained in the same tube, and the same sensors as when tracing pressures in the upper airways.

The internal thermistors/pressure transducers (Camtip, Camtech a/s) are contained in a silicone tube 1.9 mm in diameter. This includes four to six sensors, and the sensors in the hypopharynx and the epipharynx were chosen to monitor airflow as well as pressure. Standard polysomnograms can be performed at the same time that internal airflow is measured.

Measuring airflow by internal thermistors is more sensitive to minor changes in flow and eases the diagnosis of hypopneas in patients suffering from sleep-related breathing disorders.

Indications for, and benefits from the use of, internal airflow measurements of the upper airways will be illustrated by clinical examples and abstracts of clinical studies performed by the authors' unit.

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# DYSAUTONOMIA IN PATIENTS WITH MILD SLEEP-DISORDERED BREATHING*

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*Introduction:* Multiple studies demonstrate the interaction between obstructive sleep apnea (OSA) and autonomic dysfunction. Moderate and severe OSA are associated with autonomic test abnormalities postulated to be a consequence of the oxygen desaturation that occurs during apnea events. The authors suspect that dysautonomia is associated with a greater risk of sleep-disordered breathing. To evaluate this, they examined the relationship of patients with mild sleep-disordered breathing and autonomic dysfunction.
*Methods:* The authors studied a cohort of 20 patients with no prior diagnosis of OSA or snoring. All individuals underwent respiratory polysomnography (Autoset, Resmed, San Diego, CA), Epworth Sleepiness Scale (ESS) to evaluate sleepiness, and autonomic function testing (sweat responses and cardiovascular responses to the Valsalva maneuver, deep breathing and tilt). Sleep apnea syndrome was defined as RDI > 5 events/hour.
*Results:* Twelve of 20 individuals were diagnosed with mild sleep apnea (60%). Consistent abnormalities of measures of adrenergic dysfunction were correlated with the RDI ($R = 0.58$, $p = 0.007$). No correlations with age, oxygen desaturation, or ESS were observed.
*Conclusions:* Mild OSA is associated with abnormal autonomic indices unexplained by oxygen desaturation during sleep, sleepiness, or age. The cause of sleep-related breathing instability in patients with adrenergic dysfunction is unknown. The authors speculate that adrenergic dysfunction may affect airway collapsibility.

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# ARTERIAL BAROREFLEX DURING SLEEP*

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Respiratory disturbances during sleep are increasingly being recognized as important factors affecting cardiovascular regulation. Obstructive sleep apneas (OSA) cause marked fluctuations in heart rate and blood pressure,[1] but even minor respiratory events can significantly affect cardiovascular variables during sleep.[2]

Most studies on the pathophysiology of OSA-induced cardiovascular changes focus on the role of sympathetic activation.[1] In OSA patients, during sleep, sympathetic nervous activity progressively increases during each apnea,[3] probably in relationship to the development of hypoxemia. Sympathetic activation is considered important in the pathogenesis of the hypertensive peak observed at the resumption of ventilation, together with the arousal reaction.[1,4] Sympathetic activity is also high in OSA patients during wakefulness, when ventilation is normal, possibly due to the tonic hyperresponsiveness of peripheral chemoreceptors to hypoxic stimuli.[5] Therefore, several pieces of evidence point to a major role of the sympathetic nervous system in OSA-associated cardiovascular changes.

In normal conditions, sympathetic activity is balanced and modulated by the activity of the parasympathetic system. The arterial baroreflex is a very important parasympathetic mechanism of cardiovascular control buffering acute changes in blood pressure. An increase in blood pressure is detected by the arterial baroreceptors, causing a reflex increase in parasympathetic output to both arterial vessels and the heart: the first decreases systemic vascular resistance by blunting sympathetic activity, the second slows heart rate. A fall in blood pressure exerts the opposite effects.

Little is known about parasympathetic dysfunction in OSA, and about parasympathetic activity during sleep in general. The authors studied spontaneous baroreflex control of the heart rate by analyzing continuous blood pressure tracing obtained noninvasively (Finapres) during polysomnography. Spontaneous baroreflex control of the heart rate was identified as sequences of four or more consecutive heart beats in which the pulse interval (PI, the reciprocal of heart rate) and systolic blood pressure (SBP) linearly increased (+PI/+SBP) or decreased (-PI/-SBP).[6] Baroreflex sensitivity (BRS) was estimated as the mean slope of all sequences during nocturnal wakefulness (W), non-REM stage 2 sleep, and REM sleep. In addition, short-term variability of blood pressure and pulse interval was analyzed by calculating the mean and standard deviation of these two variables over two-minute periods of stable sleep stage. These techniques were

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applied to study normal subjects and OSA patients during sleep, in order to assess whether OSA-induced autonomic dysfunction also involves the parasympathetic system.

In normal middle-aged, non-obese subjects ($n$ = 11), short-term cardiovascular variability was low during sleep, and mean spontaneous BRS was 13.0 ± 3.1 msec/mmHg, with no major differences between sleep stages. Conversely, mean BRS during sleep in untreated OSAS patients ($n$ = 29) was 7.9 ± 2.1 msec/mmHg, a value of about 40% lower than that found in normal subjects. A direct relationship was found between mean lowest $SaO_2$ and BRS in non-REM stage 2 sleep, suggesting the role of hypoxia in baroreflex dysfunction. Cardiovascular variability was much higher in OSAS patients than in controls during non-REM stage 2 and REM sleep, suggesting that baroreflex dysfunction may contribute towards OSA-induced cardiovascular fluctuations.

In 16 OSA patients, the authors studied the spontaneous baroreflex control of heart rate during the acute application of nasal continuous positive airway pressure (CPAP). Nasal CPAP normalized blood pressure and pulse interval variability during sleep, but had only minor effects on BRS. Only the baroreflex response to hypotension (*i.e.*, the BRS in -PI/-SBP sequences) increased during sleep, while the baroreflex response to hypertension was unaffected. These results suggest that normalization of respiratory and cardiovascular variables during sleep is not enough to improve baroreflex function.

Finally, in ten OSA patients the authors obtained polysomnographic recordings before and at CPAP withdrawal after long-term CPAP treatment (mean 5.3 ± 3.8; range 2-14 months). BRS improved significantly after treatment, despite the reappearance of OSA when CPAP was suddenly discontinued. After long-term CPAP, mean BRS increased by 59% during nocturnal wakefulness ($p$ = 0.007), and by 68% during non-REM stage 2 sleep ($p$ = 0.005), but did not vary during REM sleep. These changes were associated with a lower cardiovascular variability and degree of OSA-induced hypoxemia compared to the untreated conditions, suggesting that long-term CPAP can effectively reverse OSA-induced baroreflex dysfunction, possibly through a major improvement in the level of nocturnal oxygenation.

These data augment previous observations of decreased sympathetic activity after long-term CPAP treatment.[7] Given the pathogenetic importance of intermittent hypoxia in OSA-induced autonomic dysfunction,[1] long-term treatment seems to be necessary to attenuate the increased peripheral chemoreceptor responsiveness typical of OSAS.[5] More data are needed to assess whether the CPAP-induced improvement in autonomic function is also associated with a reduction in the high cardiovascular risk reported in OSA patients.

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# USE OF MEDICAL RESOURCES BY OBSTRUCTIVE SLEEP APNEA SYNDROME PATIENTS TEN YEARS PRIOR TO DIAGNOSIS*

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*Introduction:* The authors compared the health care utilization records of 181 patients with obstructive sleep apnea syndrome (OSAS) for the ten-year period prior to diagnosis in their laboratory to those of randomized age-, gender-, and geographically-matched controls from the general population.
*Methods:* The authors analyzed data in the Manitoba Health Database, a record of all hospital stays and physician claims, complete with associated diagnoses and costs, that occur in the Province of Manitoba. They were able to determine total individual usage for each OSAS patient each year, compared to controls randomly selected from the same database and matched for gender, birth year, and area of residence. Statistical analysis of these data was performed using a two-way repeated measures ANOVA.
*Results:* During the ten-year period, all patients and more than 99% of the controls had contact with the health care system. A strong, statistically significant relationship was seen between OSAS and heavy use of health care resources in each of the ten years studied. In OSAS, use of health care resources was significantly higher in seven of ten years prior to diagnosis (see Fig. 1). OSAS patients also had more hospitalizations: they had 1118 nights (6.2 per patient) in

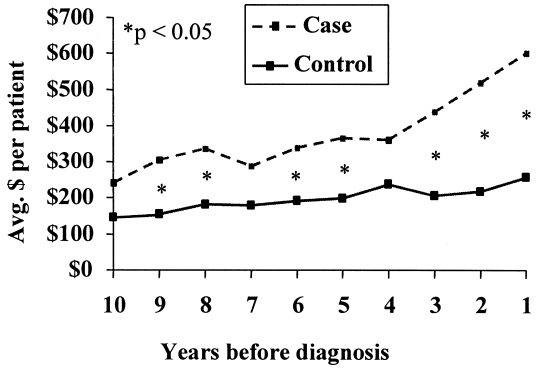


*Fig. 1.*

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hospital versus 676 nights (3.7 per person) for controls over the ten-year period. Payments to physicians for the OSAS patient group totalled $ 686,365 (Canadian) compared to $ 356,376 for the controls for the length of the study.

*Conclusions:* OSAS patients use medical resources at about twice the rate of controls as far back as ten years prior to diagnosis. Future research will examine factors determining this increased utilization, as well as the effect of treatment.

# SURGICAL THERAPY

# INDICATIONS FOR SURGERY IN OBSTRUCTIVE SLEEP APNEA SYNDROME

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## Introduction

The great variability in the surgical options available for the treatment of snoring and obstructive sleep apnea syndrome (OSAS), and the difficulty to predict the therapeutic solution, are mainly based on confused classification and clinical diagnostics (snoring, OSAS), and on the variability between individuals with regard to obstructive sites during the various stages of sleep. The site of collapse may indeed be located in one or more segments of the pharyngeal airway, with no rigid support, or between the soft palate and the epiglottis.[1,2]

Analysis of the literature has also revealed different uses for the various surgical techniques in the various segments of the involved airways, as well as the neglect of some crucial segments, variability in the definition of therapeutic success even with the help of objective indexes (apnea index (AI): apnea-hypoapnea index (AHI)), broad fluctuation in the percentage of success and frequency of complications and sequelae, and confusion between the evaluation of short- and long-term results. Moreover, the advent of new technological instruments makes it difficult to compare results, and only lately has there been greater clarity in the clinical differentiation of the various pathological stages, such as being able to define an upper airway resistance syndrome (UARS) or the EEG characteristics of microarousal/sleep-hour (MA/hS).

We think the first problem to be faced is to define which patients should be referred for surgical treatment. First of all, it should be specified that, before any surgical treatment, the patient must have undergone polysomnographic study. If that study does not reveal an abnormal AI or AHI/hS, hygienic measures for sleep and daily life (weight loss, abolition of alcohol and smoking) must be the first therapeutic choice. If, indeed, the results of the polysomnographic study are normal and minimum snoring is present, and the patient or/and their partner request a surgical solution, our attitude should be very cautious and pru-

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dent, and we should always try to avoid any risks due to surgery on the 'innocent member' of the couple. Therefore, the simple snorer may and should present with a pathophysiological picture that can be treated with measures affecting life-style (and sleeping habits!), and it should be explained that snoring is a condition that may frequent a certain percentage of the population, according to age, sex, and body index.

If the polysomnographic data reveal an alteration in MA/hS alone, with no involvement of AI or AHI, we must classify the patient as a UARS, and also remember to include a study of the intraesophageal pressure in order to detect any possible gastroesophageal reflux.

Patients in whom the polysomnographic study reveals an alteration in Ma/hS, as well as in AI and AHI, are included in the OSAS group, which is broken down into mild, moderate, and severe. Both UARS and mild OSAS patients are candidates for surgical treatment, while more severe OSAS patients should undergo therapy with continuous positive airway pressure (CPAP).

The second point that needs to be defined is whether or not an obstructive anatomical site is present. If the ENT examination does not reveal any obstruction sites, the patient should be referred to orthodontic treatment for mandibular advancement, and should be informed that the percentage of improvement in snoring and AHI is in the range of 30-50%. The patient should also be informed about the various side-effects of oral appliances (excessive salivation, stiff temporomandibular articulation, modification of occlusion alignment). This group of appliances also includes 'nose dilators'. It is frequently pointed out in the literature that patients show a subjective improvement of symptoms, with no positive findings on polysomnographic study, except for cases of nasal valve pathology. In any event, the use of nose dilators and oral appliances in patients with mild OSAS or MA/hS alterations must be proven objectively by the polysomnographic study, so that, in case of failure, patients can be referred to other types of treatment.

However, it is important that the anatomical balance of snorers is systematically investigated for obstruction factors that modify the compliance of the oropharyngeal segment, due to increased endoluminal pressure, whether this is narrowing of the nasal segment or of the collapsible oropharyngeal segment.

Indeed, the primary goal of surgery is to correct upper airway abnormalities that may contribute to the collapse. Surgery may be indicated in primary snorers, snorers with an increased MA/hS, or in patients with mild OSAS if they present with anatomical obstructions of the upper airways. Accurate imaging of the upper airways (cephalometry, computed tomography (CT), magnetic resonance (MR), is always a prerequisite for surgery. On the other hand, the data in the literature referring to the value of such tests and their surgical implications are not homogeneous. Perhaps a unanimous consensus should be reached on the performance of a post-surgical polysomnographic study in order to assess the results of surgery. Patients treated for primary snoring could be an exception to this protocol.

### Nose surgery

As described in the chapter on "External multi-layer surgery in the treatment of OSAS" (p. 367), nose surgery is very often the first therapeutic choice in the treatment of this condition. Nasal obstruction plays a fundamental role in the genesis of snoring, since the increased nasal resistance determines a reduction in inspirational pharyngeal luminal pressure, thus facilitating the collapse of the velopharyngeal segment. Therefore, the pharyngeal surgical treatment of snoring should always be preceded and/or completed by surgery to normalize nasal resistance, the aim of which should be to normalize the geometry of the nasal cavities in order to restore physiological nasal resistance values. This group of surgical procedures includes all those operations that aim to correct nasal air obstruction, such as the volumetric reduction of turbinates, plastic surgery of the septum, rhinoseptoplasty, and functional endoscopic sinus surgery (FESS). Nose surgery is often performed in conjunction with velopharyngeal surgery. In this case, the use of nasal swabs allowing for nasal respiration is recommended.

For snorers with increased MA/hS (UARS) or OSAS patients, postoperative oximetry monitoring at night is indicated while nose packing is being employed. If alterations are detected, CPAP must be performed, although this requires a patent nasal fossa.

The application of CPAP following nose surgery may be facilitated by the use of a full face mask. However, after the packing has been removed and before the patient is discharged, care must be taken to ensure that normal nighttime oximetry has been restored. If this has become worse, home care with CPAP will be required.

### Rhinopharyngeal surgery

Adenotomy or the removal of benign neoformations of the rhinopharynx are the procedures employed in this anatomical region. Adenotomy and tonsillectomy are first-choice procedures in OSAS children if no craniofacial abnormalities are present. It is important to remember that rhinopharyngeal surgery should not be associated with concomitant velopharyngeal surgery, due to the risk of adhesions and nasopharyngeal stenosis. In children, a postoperative polysomnographic study is only mandatory if there is no clinical improvement.

### Velopharyngeal surgery

Velopharyngeal surgery includes three types of surgical procedures: uvulopalatopharyngoplasty (UPPP), laser-assisted uvulopalatoplasty (LAUP), and radiofrequency tissue volume reduction (TVR). After having informed the pa-

tient about the local effects and postoperative results on the individual symptoms, the use of analgesics and anti-inflammatory drugs plays an important role in the therapeutic protocol, together with the study of gastroesophageal reflux. It has been suggested in the literature that the improvement of subjective symptoms is around 60-80%, probably because in only about 50% of cases of obstruction disorders is the obstruction site exclusively confined to the velopharyngeal segment.[3-7] Another factor that should be considered is that efficacy tends to decrease over time and when objective evaluations are used.[8] This finding is extremely important when defining the objective parameters in objective and subjective analyses of snoring presented in the literature. For snorers with increased MA/hS, velopharyngeal surgery has non-predictive effects on these parameters, which are thought to be correlated to excessive daytime drowsiness. Also, there is no ultimate consensus on the beneficial effects of velopharyngeal surgery in relation to the decrease of MA/hS, although Boudewyns *et al.*[9] showed a significant decrease of α-EEG arousals in non-apneic snorers following UPPP. On the basis of subjective analyses, other reports described a decrease in daytime sleepiness episodes following UPPP.[10,11] The finding suggested by Rollheim *et al.*[12] is important in the selection of patients for surgery. According to these authors, velopharyngeal surgery is less effective when the patient has a body mass index greater than 28 kg/m$^2$.

The success index of velopharyngeal surgery in mild OSAS patients is approximately 40-50% on polysomnographic evaluation, provided of course that the patient does not present with any other types of upper airways obstruction.[13,14] In conclusion, velopharyngeal surgery is indicated in patients who are pure snorers, in those with increased MA/hS, and in those with mild OSAS. It is not a first-choice treatment for moderate and severe forms of OSAS.[15]

UPPP,[16,17] which is performed under general anesthesia, includes tonsillectomy if tonsils are present. It is particularly indicated in patients with a 'deep-type velum', which means that the obstruction area mainly originates from the pillars or tonsils.[18] UPPP is a combined reduction and pharyngoplasty procedure, the purpose of which is two-fold:

- vibration, to reduce the length of the velum vibrator;
- volume, indicated in cases in which there is concomitant OSAS.

However, achievement of this volume was not confirmed in the work of Polo *et al.*,[19] according to whom UPPP may stabilize the airway at an oropharyngeal level, but is incapable of increasing the cross-section of the pharynx. The main problem with UPPP is that a standard technique is performed for pathologies with a different anatomical substratum, which however share the phenomenon of snoring. The commonest mistake made is to include a patient in a predetermined surgical protocol, without tailoring that surgery to the patient's specific individual pathological anatomy.[20]

In this case too, hospitalization (48 hours) and post-surgical treatment must include clinical re-evaluation with night oximetry in OSAS patients, and possibly treatment with CPAP in case of evident desaturation phenomena. Another

important consideration is that, following velopharyngeal surgery, the edema may cause the surgical status of the patient to deteriorate in the immediate postoperative phase, thus reducing the patency of the airways.[21] This postoperative desaturation is also present in primary snorers and in UARS patients, although in these cases, it is definitely less dangerous.

LAUP is a technique that can be performed under local anesthesia.[22,23] It is indicated in patients with a flat-type velopharynx, which in this case means that the respiratory obstruction in the upper airways in particular originates in the uvula and/or the folds. LAUP is contraindicated in patients with a deep velopharyngeal anatomy, because it is not effective in tonsil hypertrophy or pillar medialization.[24] The reason for LAUP is the inflammation on the surface of the velum and pharynx. This determines centripetal fibrosis with a reduction of the soft palate, which contributes to sound vibration. From an anatomical point of view, there is no evidence to show a lengthening of the velopharyngeal isthmus after this type of surgery. In fact, some authors believe that this surgery may narrow the isthmus.[24] Mild OSAS patients treated with LAUP will have to stay in hospital for 48 hours because of the edema that may be caused by oxygen desaturation.[21] The recently proposed radiofrequeny,[25,26] aims to reduce the volume of tissue in the soft palate by means of fibrosis due to tissue protein denaturation. The indication for this is exactly the same as for LAUP, *i.e.*, patients with a flat-type palate. The advantages of this technique seem to be better control of pain symptoms,[27] and faster healing of the mucosa. RF may also be indicated to increase the stiffness of the velum following LAUP failure.

Then there are the procedures that are performed at the base of the tongue, and which include soft tissue reduction procedures, by means of the $CO_2$ laser and RF. These procedures can be suggested in primary snorers, UARS, and mild OSAS with evident obstructions at a retrolingual level.[28,29] There are also hard tissue corrective management procedures, which include hyoid suspension techniques, mandibular osteotomies with advancement of the genioglossus muscle, and maxillomandibular advancement.[30-32] These are primarily indicated in mild OSAS or in moderate and severe OSAS patients who have rejected CPAP therapy. In such cases, it is important to rely on sound imaging procedures (CT, NMR), which may indicate a specific surgical treatment. Polysomnographic study after three months may authorize the discontinuation of CPAP, while the patient will have to be informed that the success rate with this type of surgery is between 40 and 70%, according to the severity of OSAS.[30,33]

Finally, we would briefly like to mention tracheotomy, the original surgical technique used in OSAS. It still plays an important role as a protective measure in combination with retrolingual corrective hard tissue surgery and in patients with OSAS whose CPAP compliance is poor, and who cannot undergo surgery, or in whom surgery is contraindicated.

In conclusion, in this disease too, the key to therapeutic success lies in the appropriate selection of patients and in the correct indication for surgery. Once the correct indication has been established, the various techniques available will enable the successful control of a psychosocial clinical problem that, as indicated by the epidemiological data, has now reached considerable proportions and figures.

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# TREATING NASAL OBSTRUCTION IN OBSTRUCTIVE SLEEP APNEA SYNDROME

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## Introduction

The observation that nasal obstruction may affect breathing during sleep has been known for more than a century. Lavie published an excellent review of studies carried out in the 19th century.[1] As early as 1581, Levinus[2] wrote that breathing through the mouth in the supine position causes restless sleep. The first book, entitled *The Breath of Life* was published by Catlin in 1861.[3] A later edition, published in 1890, was called *Shut Your Mouth and Save Your Life*. In 1889, Guye presented a publication called *Shut Your Mouth and Save Your Brain*.[4] Cline[5] and Wells[6] first described the surgical relief of excessive daytime sleepiness following nasal surgery.

Current epidemiological data suggest a connection between impaired nasal breathing and sleep-related breathing disorders. Vainio-Mattila[7] described a strong correlation between snoring and nasal obstruction in 162 subjects. Stradling and Crosby[8] studied 1002 persons, 17% of whom were snorers. Size of neck, smoking, and subjectively impaired nasal breathing were identified as risk factors for snoring. In six of nine patients with obstructive sleep apnea (OSA), Ancoli-Israel *et al.*[9] described deviation of the nasal septum. In large samples of, respectively, 250[10] and 431[11] patients, the incidence of heavily impaired nasal breathing among Caucasian sleep apnea patients appeared to be approximately 15%.

The purpose of this review is to summarize the effect of the conservative and surgical improvement of nasal breathing on the severity of sleep-related breathing disorders, on the basis of evidence from the literature up until October 2000.

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## Conservative treatment

### *Nasal dilators*

Nasal dilators offer an alternative to surgical procedures for nasal stenosis, especially of the nasal valve. Nasal dilators can be used either intranasally (*e.g.*, Nozovent®) or externally (*e.g.*, Breathe Right®).

Four papers provide polysomnographical data for the use of internal dilators in a total of 45 patients (Table 1). Höijer *et al.*[12] found a statistically significant decrease in the apnea-hypopnea index (AHI) in ten patients with OSA. In contrast, the other groups[13-15] did not observe any statistically significant differences when using the internal nasal dilator.

*Table 1.* Effect of internal and external nasal dilators on the severity of OSA

| *Author* | *Dilator* | *n* | *AHI without* | *AHI with* | *p value* |
|---|---|---|---|---|---|
| Höijer *et al.*1992[12] | internal | 10 | 18 (AI) | 6.4 (AI) | 0.008 |
| Metes *et al.* 1992[14] | internal | 10 | 46 | 44 | n.s. |
| Kerr *et al.* 1992[13] | internal + ND | 10 | 64.9 | 63.2 | n.s. |
| Hoffstein *et al.* 1993[15] | internal | 15 | 35.4 | 33.9 | n.s. |
| Schönhofer *et al.*1997[20] | external | 30 | 38.1 | 40 | n.s. |
| Gosepath *et al.*1999[19] | external | 26 | 31.7 | 26.3 | 0.031 |

AHI: apnea-hypopnea index

Three papers show the raw data of individual subjects.[12,13,15] Only three of 35 patients met the criterion of success, as recommended by Sher *et al.*[16] (reduction in AHI of >50% and reduction to values <20), which corresponds to a success rate of only 9%.

Löth *et al.*[17] observed a significant increase in the quality of life, Petruson[18] described enhancement of sleep quality, and Kerr *et al.*[13] found a statistically significant decrease of arousals with the use of internal nasal dilators.

External dilators were studied in 56 patients with OSA and in 20 newborns (Table 1). Again, only one working group found a statistically significant reduction of AHI when using external dilators (plasters).[19] Another group did not see any statistical differences.[20] Since no raw data were provided in these studies, no overall success rate can be given. No predictive criteria could have been defined by the authors. Scharf *et al.*[21] studied newborns aged from two to four months, and noted a statistically significant decrease of AHI from 3.2 without to 1.2 with Breathe Right® nasal plasters.

In accordance with the results on internal dilators, Schönhofer *et al.*[20] noted an improvement of sleep quality and daytime well-being after the use of external dilators. Patient compliance was specified at 86.7%. Pertinent data were provided by Scharf *et al.*[22] In nine simple snorers, they noted an improvement

in the quality of sleep and sleep efficacy with the use of Breathe Right®. Using external dilators, Di Somma *et al.*[23] only detected improved nasal airflow during inspiration. In contrast, external dilators combined with decongestive nasal drops augmented nasal airflow during both inspiration and expiration. No long-term results (studies) on nasal dilators are available.

*Topical steroids*

In 20 patients with seasonal allergic rhinitis, topical steroids were able to improve the subjective parameters sleep quality, daytime sleepiness, and nasal breathing.[24] Up to the present, there are no objective data concerning this issue.

*Nasopharyngeal tubes*

In 1981, Afzelius *et al.*[25] had already reported two cases of severe OSA cured by self-intubation with a nasopharyngeal tube. Within a follow-up period of six months, no complications were found.

Nahmias and Karetzky[26] treated 44 patients with OSA with nasopharyngeal tubes. At four months' follow-up, 44% of the patients were still using their tubes. The apnea index (AI) was decreased by 62.3%. The success rate was quoted 36.4% in this study, which is superior to rhinosurgical procedures and nasal dilators. Bridging of the nasopharyngeal segment would seem to be the cause of this superior success rate, since the nasopharynx is not treated by rhinosurgery or nasal appliances.

## Surgical treatment

What effect do rhinosurgical procedures have on the severity of sleep-related breathing disorders? There are some case reports of OSA only being able to be cured by nasal surgery.[27,28] On the other hand, in 1977 Simmons *et al.*[29] had already reported cases in which no improvement of objective parameters was seen, despite substantial increases in subjective nasal breathing.

There are only nine further publications on this topic, which deal with the severity of pre- and postoperative OSA (see Table 2). In total, 130 patients from eight different working groups were assessed.[30-38] The postoperative examination period was short, extending from one[30] to 44[32] months. With the exception of the oldest of these studies, which describes a significant postoperative reduction in AI from 37.8 to 26.7 in a total of nine patients, no other working group was able to determine a significant reduction in the severity of OSA for their respective group of patients (see Table 2). In four studies, in which a total of 58 of the 130 patients were included,[33,36-38] even increases in AHI and AI were found. However, these changes were not significant either.

*Table 2.* Effect of nasal surgery on the severity of OSA

| *Author* | *n* | *Follow-up* | *AI pre-* | *AI post-* | *AHI pre-* | *AHI post-* | *p value* |
|---|---|---|---|---|---|---|---|
| Rubin *et al.* 1983[30] | 9 | 1-6 | 37.8 | 26.7 | | | <0.05 |
| Dayal and Phillipson 1985[32] | 6 | 4-44 | | | 46.8 | 28.2 | n.s. |
| Caldarelli *et al.* 1985[31] | 23 | no data | 44.2 | 41.5 | | | n.s. |
| Aubert-Tulkens *et al.* 1989[33] | 2 | 2-3 | 47.5 | 48.5 | | | n.s. |
| Sériès *et al.* 1992[34] | 20 | 2-3 | | | 39.8 | 36.8 | n.s. |
| Sériès *et al.* 1993[35] | 14 | 2-3 | 17.8 | 16.0 | | | - |
| Utley *et al.* 1997[36] | 4 | no data | | | 11.9 | 27.0 | - |
| Verse *et al.* 1998[37] | 2 | 3-4 | 9.2 | 47.3 | 14.0 | 57.7 | - |
| Friedman *et al.* 2000[38] | 50 | >1.5 | | | 31.6 | 39.5 | n.s. |

AI: apnea index; AHI: apnea-hypopnea index

Verse *et al.*[37] reported that the severity of OSA increased substantially in two patients who had been operated on for massive nasal polyposis. Although adequate mouth respiration was re-established, the AHI rose from 14 preoperatively to 57.7 postoperatively. Both patients developed severe OSA with corresponding symptomatology, which had not existed preoperatively, and both required nasal continuous positive airway pressure (CPAP) treatment postoperatively. Dagan[39] describes a similar course in two cases after septorhinoplasty.

However, Lavie *et al.*[40] noted a significant reduction of arousals and a highly significant reduction of daytime sleepiness in a group of apneics after septoplasty. Despite the fact that there was no polysomnographically measurable improvement of OSA in their study group, 12 of 14 patients also felt less tired during the day and exhibited better sleep quality.[41] These results indicate that the reduction of daytime sleepiness and the improvement of sleep quality do not depend on the severity of a sleep-related breathing disorder, since significant changes were also found when simple snorers and patients with OSA were assessed separately. Accordingly, similar results were achieved after optimizing nasal ventilation in simple snorers.[18,42]

Although it would seem to be true that, in a group of patients, it was impossible to achieve improvement of OSA by successful nasal surgery, some individuals recovered from OSA after nasal surgery only. Unfortunately, in the literature different criteria have been applied for measuring success. For this reason, data in the literature vary between 0%[33,37] and 33%.[32] Using the raw data available for 57 patients, an overall success rate of 18% was calculated based on the very strict criterion of success recommended by Sher *et al.*[16]

Based on these somewhat sobering results, the question arises as to whether nasal surgery is still justified as a viable option in the treatment of OSA. However, the efficacy of nasal surgery in patients who will have to undergo nasal CPAP therapy is indisputable. It has been sufficiently proved that the postoperatively required nasal CPAP pressure can be substantially decreased by nasal surgery.[11,38]

## Conclusions

In summary, it should be stated that nasal surgery cannot generally be recommended as the first choice of therapy for OSA. When compared to other surgical methods, the success rate is too low, with a value of less than 20%.

Nevertheless, there does seem to be a small proportion of patients who do respond to nasal surgery, but there are no reliable criteria for the preoperative identification of these patients.

Independent of the AHI, nasal surgery significantly improves the daytime sleepiness and sleep quality of patients with sleep-related breathing disorders. Moreover, nasal surgery still remains a valuable intervention for patients who will have to undergo nasal CPAP therapy.

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# NASO-MESOPHARYNGEAL PATHOLOGY AND SNORING

## Incidence and surgical treatment

G. Sulsenti

Most cases of nocturnal sleep apnea are secondary to or caused by neglected or incorrectly treated chronic snoring. However, in a considerable number of cases, the condition is caused by nasal breathing disorders. Thanks to advanced rhinological studies and extensive experience, we can now carry out a more accurate clinical examination of snorers and provide more timely and targeted treatment. In the past, treatment was mainly focused on symptom relief, while we can now adopt a very targeted surgical approach for treating, maintaining and restoring the normal anatomy and physiology of the organs responsible for snoring.

The first insight into the importance of nasal breathing dates back to a law scholar called Catlin who, in 1860, published his observations on the philosophy of North-American Indians. They believed and taught their children that nasal breathing is the key to life and physical well-being. Later on, in 1889, Guye from Amsterdam described attention and memory disorders in patients with severely impaired nasal breathing. In 1892, Cline and Carpenter reported cases of sleep disorders, insomnia, nightmares and cerebral impairment, due to insufficient ventilation caused by obstructive nasal pathology. Major scientists investigating the relationship between nasal function and sleep disorders collected many pathological findings in those years.

In the second half of the last century, some neurologists made a misleading but fully justified observation about obesity-related chronic pulmonary hypoventilation. Khulo and Coccagna said this was due to upper airway obstruction, and used tracheotomy to treat their patients. This surgical treatment was easy and fast, but did not relieve the underlying obstruction. It consisted of opening a passage downstream to make airflow to the lungs easier and give long-lasting results. However, these authors provided evidence that sleep disorders originate in the upper airways and not in the central airways, which up to then had been considered responsible.

Lugaresi carried out many in-depth studies on sleep and nocturnal apnea, and emphasized the primary role of craniofacial surgery in the treatment of

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these conditions and of general medicine in the treatment of endocrine and metabolic disorders.

Ever since, based on the studies and experience of the above-mentioned authors, these diseases have been treated by the relevant specialists, in order to prevent the very serious and even fatal consequences that these conditions can cause.

Neurological research and experience has shown that the area above the trachea is responsible for many sleep disorders, and even for very severe apnea. Internists and head surgeons have accepted this challenge and started to analyze the symptoms, causes, and effects accurately, in order to develop more sophisticated, targeted, and less aggressive strategies to relieve the condition and improve the quality of life and physical and mental well-being of these patients.

After developing a rationale, individual diagnosis and treatment were refined and targeted. The examination must be very accurate, all the way from the lower airways (and tracheotomy) to the nose and its physiological function, in order to adopt the best and most rational approach. Confining sleep and breathing disorders to the nose would be limiting and incautious. A step-by-step and targeted analysis can help identify causation mechanisms, and a reasonable level of risk in treating the condition is acceptable, bearing in mind that very aggressive solutions can sometimes make the situation worse.

Many studies have been carried out on the shape of the nose (cosmetic surgery) and on the role of the anterior nasal cavities, in order to identify the physiological functions responsible for air heating and moisturizing. However, the posterior tract running from the tails of the turbinates to the pharyngeal velum has not been extensively studied. This is a set of interdependent structures and organs that do not produce evident symptoms when affected by different disorders, *i.e.*, inflammation, malformation, tumors, and iatrogenic conditions, and the symptoms only tend to occur when the situation has become irreversible.

While Catlin described the preventive philosophy of American Indians, 100 years later Cottle developed and taught the physiological approach to surgery to be adopted for treating these neglected, important, and difficult conditions. We are talking about the naso-mesopharyngeal tract, a crucial junction for conditions which, at their onset, are almost always diagnosed and treated as psychosomatic disorders.

The following conditions may originate in that area: ethmoidal and sphenoidal pathology, stenosis caused by the lower turbinate tails and hyperplasia of the tubal rim, adenoid obstruction and hyperplasia as a primary condition or caused by thick secretions, the altered naso-pharynx/velum relationship, which is so important because it induces frequent swallowing and generates foreign body reactions in the pharynx, the feeling of a ‘scratchy throat’ which is very challenging socially and can often lead to pharyngeal snoring.

The literature is full of different classifications and definitions of snoring/

apnea, central and peripheral forms, influence of age, sex, weight and abdominal volume, but there have been very few studies classifying snoring according to its sound, which depends on the causes of the troublesome phenomenon. The sound produced by snoring has an important social impact on non-snorers who have to suffer long-term exposure.

All these factors should be taken into account when providing a definition and a predictive classification of the disease.

In 1972, at a specialized conference on the topic, a demonstration was organized to confirm the site of origin and the fundamental role played by the ENT surgeon in many such cases. The snoring sound varies according to the organ where it is produced. Similarly to sleep, which is affected by posture, body weight, and the central or peripheral origin of the disorder, the snoring sound varies according to whether it comes from the nasopharynx and the velum, the palate and the tonsils, the oropharynx (children), the tongue base and the hypopharynx, or the epiglottis and the laryngeal vestibule. However, each form has a different origin and must be tackled with a different and more or less risky and invasive surgical strategy.

It is worthwhile looking at the implications of the various clinical and photographic findings (Figs 1-20), in order to develop the right approach to the nasal cavities and the pharyngeal area and solve the problem from its very onset.

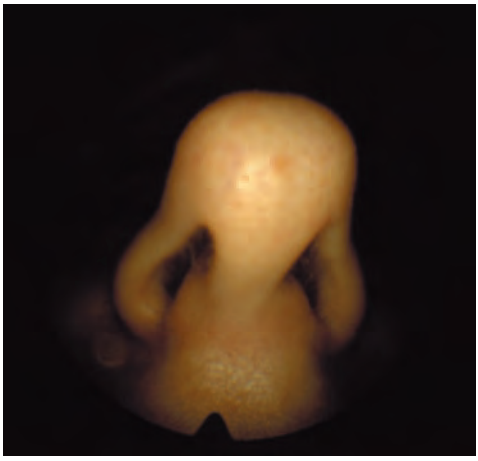

*Fig. 1.* Boxy tip with altered expiratory resistance. Inspiratory disorders are mainly due to the deformity of the columellar foot.

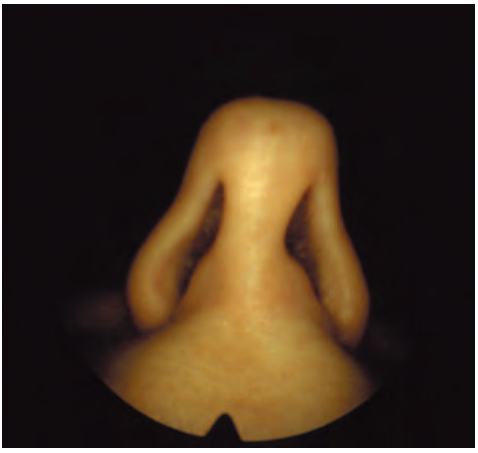

*Fig. 2.* Slit nostrils and altered columellar foot, leading to valve collapse and negatively affecting resistance.

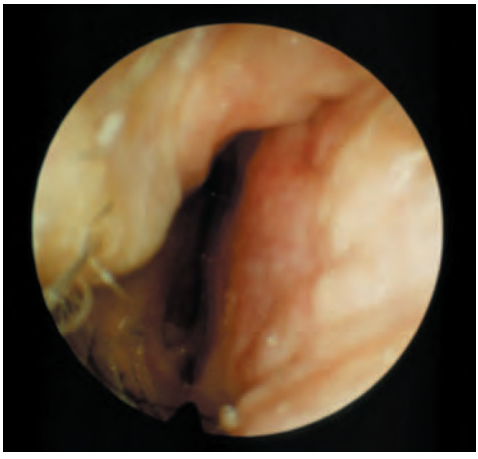

*Fig. 3.* Valve disorders due to structural deformity and secretions.

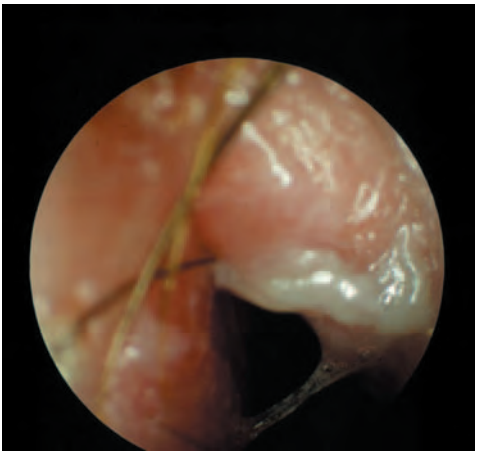

*Fig. 4.* Minck's valve collapse and limited airflow in the lower tract. Secretions are affected by the vestibular turbulence.

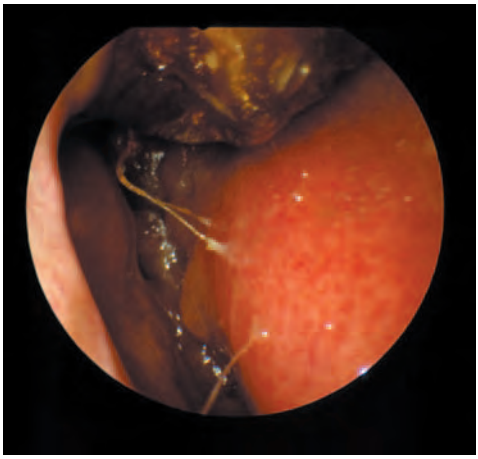

*Fig. 5.* Pathology of areas 3 and 4 causing unilateral obstruction.

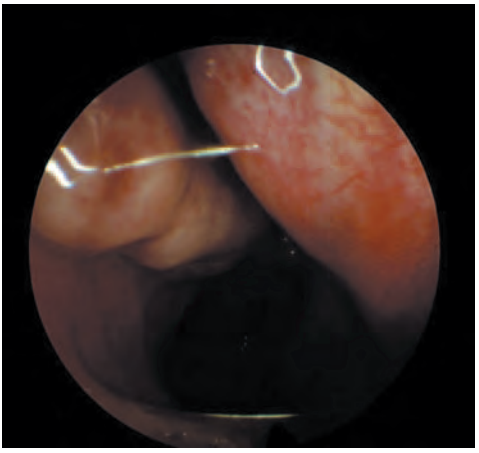

*Fig. 6.* Turbinate resection channelling airflow onto the floor.

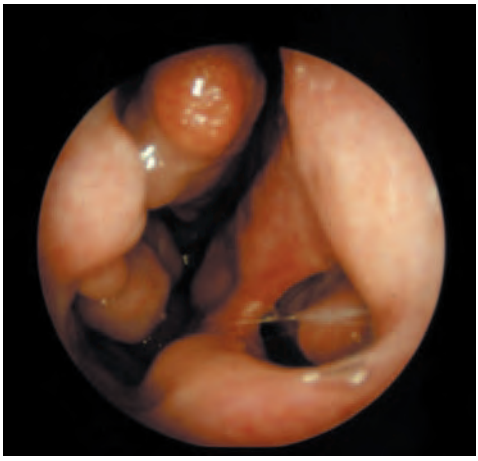

*Fig. 7.* Iatrogenic alterations of the lower turbinate body and tail, middle turbinate hyperplasia and septal perforation may cause an unpredictable increase in resistance upstream of the oropharynx.

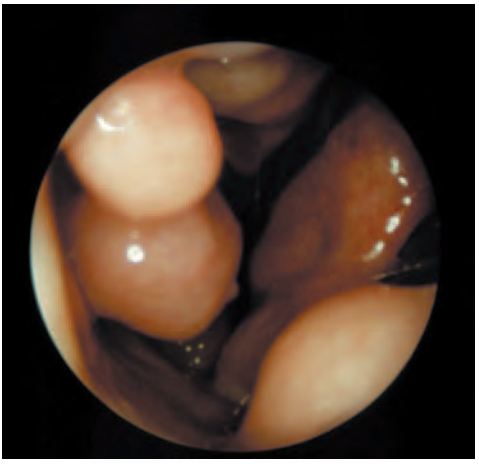

*Fig. 8.* Turbinate tail hyperplasia can obstruct the choanal current.

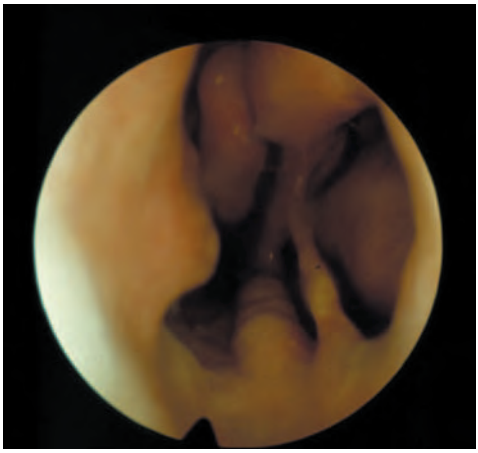

*Fig. 9.* Pituitary atrophy-dystrophy and major alterations in the posterior septum can explain the nasal origin of resistance disorders.

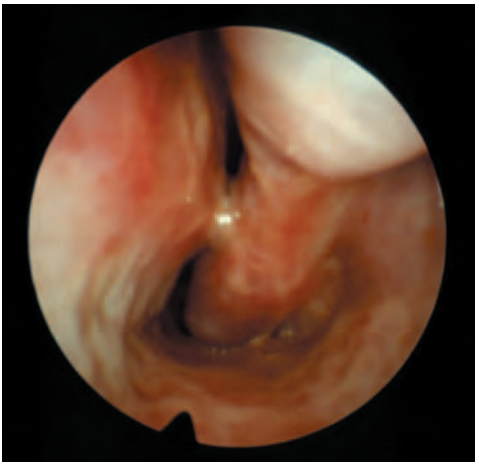

*Fig. 10.* Turbinate resection of the posterior third and the tail, especially if complicated by synechiae, can cause ultimate breathing problems during sleep.

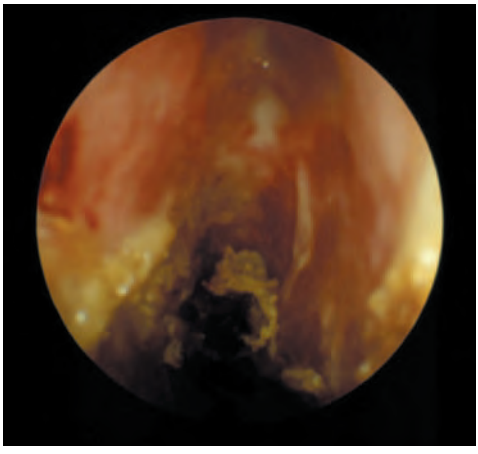

*Fig. 11.* Severe dystrophy and crusts in the nasopharynx can negatively affect the medical and surgical strategy.

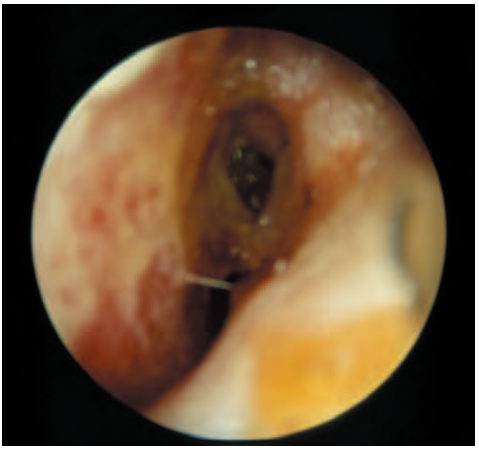

*Fig. 12.* Posterior stenosis must be treated with a targeted approach to the affected anatomical segment, in order to avoid further local complications which can lead to devastating septal perforations.

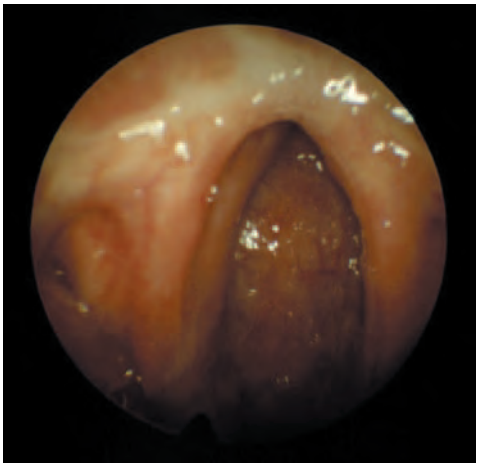

*Fig. 13.* Lack of symmetry and different airflow capacity can also be considered a disease.

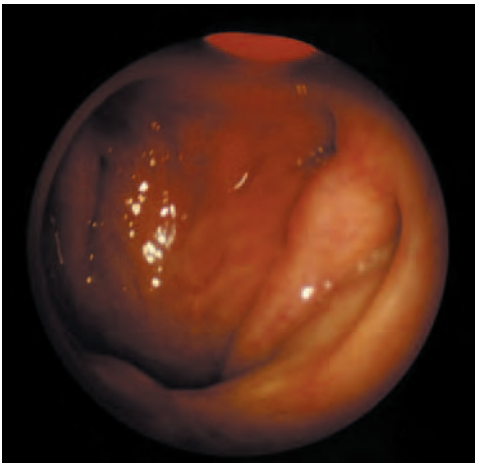

*Fig. 14.* Alterations in adenoid tissue shape and size can account for upper airway snoring.

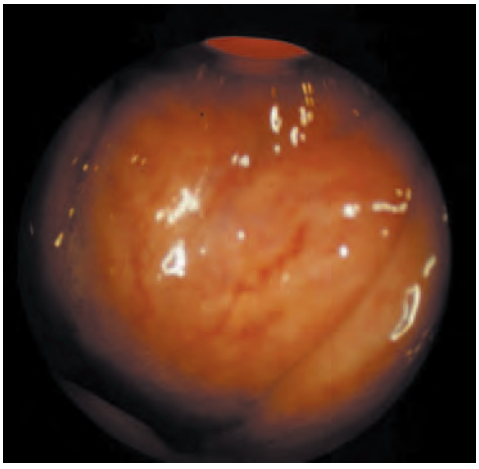

*Fig. 15.* The condition of the lymphatic system and the presence of subacute inflammation due to bacterially infected mucus stagnation in the posterior nasal cavity can have a major impact on volume.

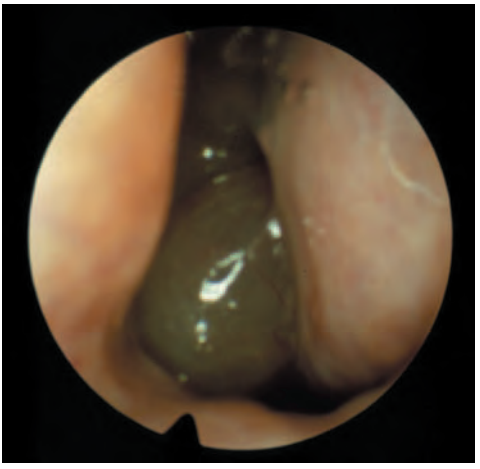

*Fig. 16.* Mechanical obstacles such as posterior ethmoid and paranasal sinus mucosal hyperplasia can cause evident problems.

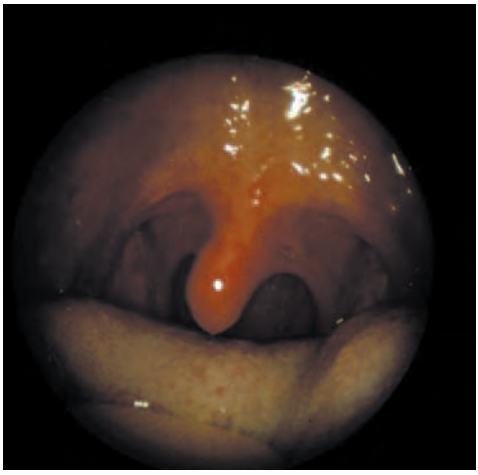

*Fig. 17.* Posterior pillar prolapse, azygohypertrophy, uvular edema or hyperplasia, and stenosis can cause troublesome snoring.

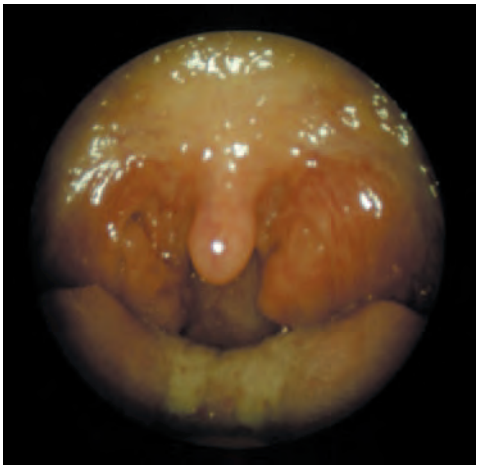

*Fig. 18.* When the tonsil lymphatic tissue is enlarged, an extended surgical strategy must also be adopted in children.

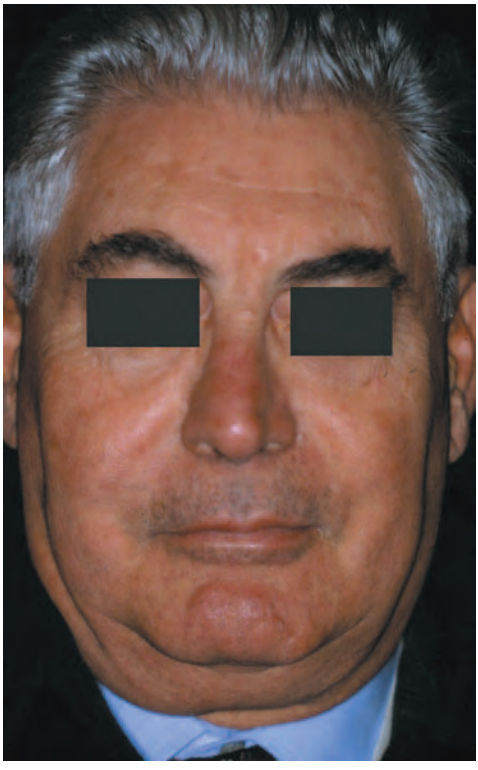

*Fig. 19.* Tongue and neck volume, position and range of movement, cannot be neglected.

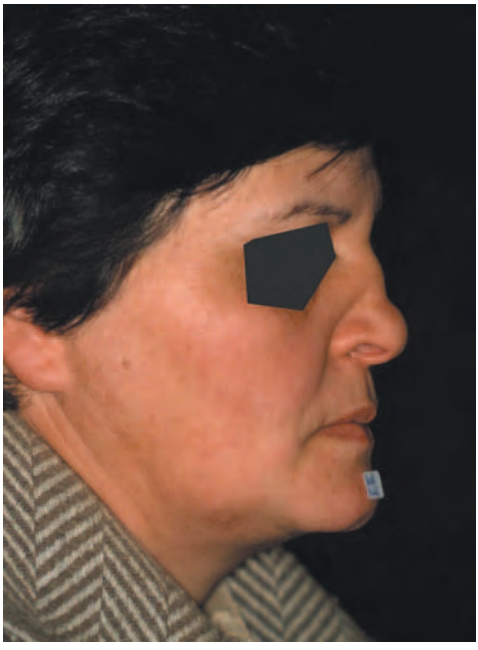

*Fig. 20.* In a number of cases, resection must be accompanied by adequate cosmetic surgery, which always has a positive psychological impact on the patients.

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# TURBINATE SURGERY BY RADIOFREQUENCY FOR SLEEP-DISORDERED BREATHING

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## Introduction

Snoring can be a sign of an obstructive breathing disorder and, since simple snoring can become loud habitual snoring and then proceed to obstructive sleep apnea syndrome (OSAS), the treatment of this condition must be taken seriously.

Although the source of snoring is primarily at the palate region, the nose and base of the tongue can also create noise. The rationale for nasal surgery in cases of snoring and OSAS is to provide the patient with a free nasal airway during sleep. The indications for nasal surgery include obstruction and abnormal airflow due to deviation of the septum and enlarged turbinates.

Surgical techniques for the inferior turbinates are a vexing problem. Although the right procedure is chosen from time to time, nowadays most rhinologists use functional nasal surgery to preserve the surface functioning of the turbinate. Functional surgery, like submucosal resection with or without lateral displacement (Legler) and turbinoplasty, is complex because it is commonly performed under general anesthesia, nasal packing is necessary, bleeding is abundant, and there is a high percentage of failure. Electrocautery, cryotherapy and laser cautery have all been used with varying effects.

Recently, functional nasal surgery has included radiofrequency energy (RFe) for submucosal tissue ablation of the hypertrophied inferior turbinates. Radiosurgery is a procedure that uses high-frequency radio waves. The impedance to the passage of radio wave energy through the tissue generates heat within the cells, which boils the tissue water, thereby creating steam and resulting in coagulation of the tissue.

Since March 1998, 242 patients with inferior turbinate hypertrophy have undergone bipolar submucosal ablation using RFe. We reported our preliminary results at the First International Workshop on endonasal laser surgery, in

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Troina (Italy).[1] Other authors have reported on this procedure.[2-6] The results of these studies demonstrate that radiofrequency tissue volume reduction (RFTVR)[3] is associated with minimal adverse effects.

## Material and methods

Two hundred and forty-two patients with inferior turbinate hypertrophy underwent bipolar submucosal ablation using RFe. Of these, 14 patients had a history of habitual snoring for many years and mild OSAS, and therefore they underwent other procedures at the same time: radio-assisted uvulopalatoplasty (RAUP), submucosal radio-assisted uvulopalatoplasty (SRUP), or myotomy and hyoid suspension (MHS). All patients underwent a complete history and physical examination.

The procedure was performed under local anesthesia, or under general anesthesia when septoplasty was being performed at the same time.

The needles were inserted into the inferior turbinate longitudinally; RFe was delivered at a power of 20 W; two to ten seconds' exposure time was used until visual blanching occurred. During removal of the needles, a short spurt of exposure caused superficial coagulation, thereby avoiding or minimizing bleeding.

## Results

Radiosurgery is a simple procedure for patients under local anesthesia. No significative pain, epistaxis or headache were observed. No packing was required when radiosurgery was performed without septal surgery. No complications were observed after surgery. Healing was rapid.

Patients used a visual analog scale (VAS) to grade nasal obstruction preoperatively and at four weeks post-surgery. The VAS (0-10) decreased from 7.5 $\pm$ 1.5 to 1.5 $\pm$ 1.5.

Most patients reported improvement of nasal obstruction. In only five cases was the result unsatisfactory, and so these patients underwent the same procedure again on one side, with good results.

## Discussion

The potential advantage of RF tissue ablation for inferior turbinate reduction is the minimally invasive technique that uses a relatively lower power and tissue temperature, which leads to reduced pain and severity of any complications, and thereby avoids any general anesthesia or additional costs.

The degree and frequency of nasal obstruction reported by patients decreased following RF tissue ablation of the inferior turbinate.

We used RFe in sleep-disordered breathing to reduce complications due to nasal packing, such as increase of the respiratory disturbance index (RDI) and duration of apnea after general anesthesia. The procedure was safe and well tolerated. Submucosal ablation of the inferior turbinate with RFe is effective for reducing nasal obstruction secondary to turbinate hypertrophy.

## Conclusions

In conclusion, our two-year experience of treatment of the inferior turbinate by radiofrequency showed many advantages: the surgical technique is relatively simple; patient compliance is good; the procedure is fast; there are no complications; no packing is required; the results are good; and, the costs are low.

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# THE ROLE OF FUNCTIONAL SEPTOPLASTY AND SUBMUCOUS DIATHERMY OF THE LOWER TURBINATES IN SNORING

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## Introduction

Variable degrees of snoring occur in about 45% of the adult population. In patients affected by airway obstruction, the rate of snoring ranges between 42 and 57.3%.[1,2] Nasal obstruction can be related to many pathologies and the spray nasal test[3] and/or the use of nasal dilatation[4] are useful tools for predicting whether nasal surgery will be beneficial in improving or eliminating snoring.[1,5-10]

The aim of this study was to evaluate the role of functional septoplasty and submucous diathermy of the lower turbinates in the treatment of snoring.

## Patients and methods

This series consists of 61 patients who underwent septoplasty and submucous diathermy of the lower turbinates between January and December 2000. There were 42 males and 19 females with a male/female ratio of 2.21/1; their ages ranged between 14 and 62 years (average, 30.8 years).

In order to assess snoring before and after surgery, a questionnaire was distributed to each patient to be filled with the partner and/or relatives. Snoring was graded according to a visual analogue scale:

0 = no snoring
1 = mild snoring
2 = medium snoring
3 = heavy snoring
4 = unbearable snoring

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## Results

Snoring was present in 45 (73.8%) of the 61 patients suffering from airway obstruction, as follows:
– unbearable in 11 patients (24.4%)
– heavy in 17 patients (37.8%)
– medium in ten patients (22.2%)
– mild in the remaining seven patients (15.5%)

After nasal surgery, the 11 patients with unbearable snoring presented with medium snoring. In the heavy snoring group, 13 cases (76.4%) showed medium and four (23.6%) mild snoring. In the ten patients who were medium snorers, two showed no improvement (20%), while mild snoring persisted in four (40%) and complete disappearance of the disturbance occurred in the remaining four (40%) patients. With regard to the seven patients who were mild snorers, three subjects (42.9%) became totally asymptomatic and four (57.1%) showed no modifications (Fig. 1).

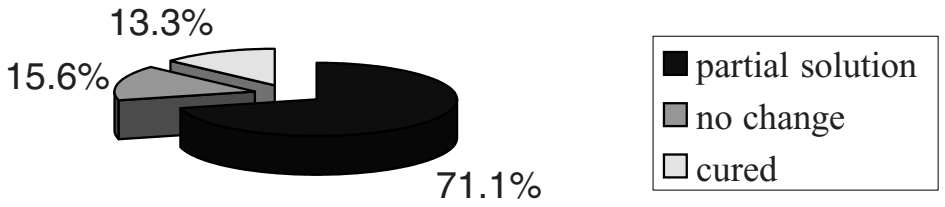


*Fig. 1.* Changes in simple snoring after septoplasty and submucous diathermia of the lower turbinates.

## Discussion

Uvulopalatopharyngoplasty is the elective treatment for snoring. Recently, septoplasty has gained increasing interest. Low[5] reported improvement in 50% of cases; in their clinical series, Ellis *et al.*[6] observed the complete disappearance of snoring in 31%, while remarkable improvement was obtained in 57% of cases (total 88%), which underlines the fact that in all cases of nasal polyposis snoring was resolved. Elsherif and Hussein[7] reported a partial response in 40% of their patients and complete success in 50%. According to Piche and Gagnon,[8] the best results are obtained with septoplasty associated with uvulopalatopharyngoplasty (97% of cases).

In cases of obstructive sleep apnea, the results are less satisfactory. Friedman *et al.*[9] reported a snoring improvement rate of 34%, and nasal obstruction was considered by Virkkula *et al.*[10] to be a complication.

There is a clear relationship between nasal obstruction and snoring. Our results are in agreement with those found in the literature. After nasal surgery

we noted an effective improvement in 71.1% of cases, complete disappearance of snoring in 15.6%, and only 13.3% of patients showed no change in their presurgical status. The most significant result was the improvement obtained in all cases of heavy snoring, whilst in mild and medium snorers, no modifications in the symptomatology were seen in 57.1% and 20%, respectively. This is probably related to the fact that, even though septoplasty can modify the airflow through the nasal cavity, many other factors are involved in the oscillation or collapse of the upper airway wall.

The relationship between snoring and nasal obstruction is a complex phenomenon, often unpredictable; however, in patients with septal deviation and snoring, significant improvement can be achieved with nasal surgery.

We believe that surgery of nasal obstructions should be considered the first treatment to be adapted in the management of snoring, either alone or in association with uvulopalatopharyngoplasty.

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# EXTERNAL MULTI-LAYER SURGERY IN THE TREATMENT OF OBSTRUCTIVE SLEEP APNEA SYNDROME

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## Introduction

It has now been established that the mechanism responsible for obstruction of the upper airways in obstructive sleep apnea syndrome (OSAS) is multifactorial, from an etiopathogenetic point of view. Thus, in patients with moderate or severe OSAS, obstructions may be observed at different levels of the upper airways. Consequently, a 'multi-layer' surgical approach targeting the various anatomical sites responsible will definitely have a greater likelihood of success. It will also avoid recourse to useless and potentially harmful additional anesthesia. Riley *et al.*[1] were the first to advocate the concomitant practice of multi-layer surgery in patients in whom the presence of multiple obstructive sites could be hypothesized. Although they initially described hyoid suspension and lower sagittal osteotomy techniques, these were not normally practiced because of their technical complexity. Today some of these procedures have been reviewed, thanks partly to the help of new technology (*e.g.*, the repose technique or radiofrequency in ablation of the base of the tongue), and such techniques have become extremely widespread.

As stated in another chapter, the choice of surgery must be based on the degree of OSAS and the location of the obstructive site. Although subjective and objective instrumental improvement after uvulopalatopharyngoplasty (UPPP) alone occurs in only 40% of cases,[2] this percentage almost doubles if the technique is combined with other surgical procedures that also involve the base of the tongue.[3,4] Thus, we believe that *multi-layer pharyngeal surgery* (which would include UPPP, myotomy of the supra- and infrahyoid muscles, tongue advancement techniques and, in a broader sense, palatal advancement) could, in principle, be indicated in patients with an apnea index (AI) or apnea/hypopnea

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index (AHI) greater than 20. Of course, the predominant level of obstruction must first be defined, and to this end, Müller's maneuver is definitely an important clinical tool. Indeed, this maneuver has a predictive value in defining the obstruction of both the palate and the base of the tongue, as well as the lateral pharyngeal wall. On this basis, tongue base surgery is indicated when its collapse reduces the airway cross-section by over 50%. However, it is mandatory that this surgery be preceded, whenever necessary, by nasal resistance correction. Moreover, patients must always be involved in decision-making and in the choice of surgical strategies.

Therefore, recourse to major external surgery in OSAS is now mainly reserved for patients in whom treatment with UPPP and laser-assisted uvuloplasty (LAUP) has not been successful, compared to the positive results obtained in the treatment of snoring, because, in many patients, the upper pharynx or retropalatal component continues to cause an obstruction.[5]

From a conceptual point of view, the UPPP techniques proposed for dealing with failures hoped to improve results by removing greater amounts of tissue in the palate and velopharynx. Efforts were then made to enlarge the airway by completely removing the palatopharyngeal muscles.[6] However, this aggressive surgical approach did not produce the expected improvement in percentage terms; instead, it only caused a greater incidence of complications, correlated with palatopharyngeal dysfunction.[7] One of the goals of surgery for the treatment of OSAS is to keep the airways unobstructed during sleep, without causing pathological alterations in speech or swallowing. Pharyngeal surgery is indicated in the treatment of apnea, because it increases the airway's diameter and decreases its collapsibility. Changes in the airway's shape and constant length are also significant. Therefore, improvements obtained in the treatment of snoring should not be confused with improvements obtained in OSAS. As snoring is mainly an alteration of the palate, UPPP is likely to improve its clinical picture by shortening and stiffening the palate, which behaves like a flutter valve if it is not modified.[8]

OSA is very frequently the result of multiple collapses of segments of the airway, which require enlargement in order to prevent obstruction of flow. It has been hypothesized that, in OSA patients, especially in those in whom UPPP has failed, the determining pathological factor is caused by lower pharyngeal obstruction. After all, many untreated patients suffer from a retropalatal obstruction (50-80%) and the retropalatal airway segment becomes the primary site of nocturnal airway obstruction.[9-11] Since the palate and velopharynx are critical sites, it is not surprising that obstruction and collapse often persist at the level of the palate after unsuccessful treatment with UPPP.[12,13] Potential surgical strategies proposed to increase the retropalatal space, and hence the oropharyngeal volume, have included ablation of redundant oropharyngeal tissue (tonsils, velum), shortening of the soft palate, increasing the stiffness of the lateral pharyngeal wall, and palatal skeletal advancement. Increased oropharyngeal volume due to soft tissue resection risks causing damage to the

velopharynx, since UPPP is a surgical procedure only involving the soft tissues. The efficacy of UPPP is countered and sometimes invalidated by the special anatomical reactivity and the risk of velopharyngeal complications, which often can be neither predicted nor envisioned. An alternative could be to enlarge the retropalatal airway segment by transpalatal advancement pharyngoplasty. Patients who were previously subjected to UPPP, but who refused maxillofacial advancement, could thus be candidates for transpalatal advancement pharyngoplasty.[14]

## Suprahyoid myotomy

The first external approach reported by Riley *et al.*[1] was performed on the skeletal structure supporting the hypopharynx. They employed a technique already in use at the time, namely laryngeal suspension, originally performed for the correction of laryngeal aspiration following supraglottic laryngectomy. The original technique called for the removal of the hyoid muscle, and the suspension of the hyoid bone on the mandibular arch by means of the fascia lata. After a number of modifications and simplifications, the technique now involves the release of the hyoid bone from the subhyoid muscles (the sternohyoid and sternothyroid muscles), and the subsequent anterior and inferior advancement of the hyoid bone above the thyroid cartilage. This causes stretching and elongation of the hypo-epiglottal ligament, thereby increasing the diameter of the hypopharynx.

The technique provides for a horizontal incision at the level of the body of the hyoid bone over its entire length. An incision is thus performed on the skin, subcutaneous tissue and platysma, and the strap muscles are exposed. The strap muscles are divaricated to expose the hyoid bone and thyroid cartilage. With electrocautery, the superior attachments of the sternohyoid and sternothyroid muscles are released to the hyoid bone; the suprahyoid musculature is then lysed between the cornua, enough to allow the passage of a large needle to the upper body of the hyoid bone. The inferior strap muscles are then divided vertically in the midline for a short distance in order to expose the cartilage. An Allis clamp is placed on the central body of the hyoid for retraction, and a No. 2 wire and needle, made of non-resorbable material, is passed around the hyoid about 1 cm laterally to the midline. After this needle has been retrieved, it is then passed through the ipsilateral thyroid ala, approximately 1 cm from the notch, and 1 cm from the alar border. A second suture is placed on the same side, starting at the level of the lesser cornu and ending 2 cm from the thyroid notch, and 1 cm from the thyroid border. This sequence is repeated on the opposite side. The four sutures are then carefully tied, while downward inferior traction is applied to the hyoid bone to minimize tension during closure. It is helpful to apply a non-serrated clamp to the first knot, in order to maintain it tightly fastened until the second knot can be secured. The wound is irrigated, drained and closed in layers, and is followed by a pressure dressing.

**Mandibular osteotomy with tongue advancement**

This technique is a limited rectangular mandibular osteotomy for advancing the genioglossus muscle anteriorly, thereby enlarging the retrolingual air space. A gingivolabial sulcus incision is performed at the level of the insertion of the canines on both sides, and the anterior face of the mandible is exposed up to the lower margin with a Freer elevator. A 9 × 20 mm rectangular mandibular osteotomy is performed using a two-hole sagittal saw blade. This osteotomy should be a minimum of 8 mm above the inferior margin of the mandible, in order to prevent weakening of this bone, and thereby to minimize the risk of fracture of the mandible. The upper edge of the osteotomy should be as high as possible without injury to the roots of the teeth, and angled slightly upward in order to ensure that the genioglossus muscle is incorporated. Digital palpation of the genioglossus insertion at the genial tubercle is helpful at this point in order to ensure that osteotomy is correctly positioned. It is important to keep the paired osteotomy cuts parallel, so that the inner table osteotomy is the same size as the outer table one. When the osteotomy cuts are complete, a 1.5-mm drill hole is placed in the center of the bone fragment, through the outer table only. An 11 × 20 mm screw is positioned, and grasped with a 'stud clamp' specially designed for this purpose. The fragment is patiently advanced along the full thickness of the mandible and rotated in both directions.

Then the outer table of the mandible and the marrow space are removed and the fragment that remains is secured to the lower edge of the mandible with a lag technique using an 11-mm screw. The surgical field is then irrigated and the incision line sutured with absorbable material.

**Transpalatal advancement pharyngoplasty**

Accurate patient selection is crucial to the success of this technique. Patients presenting with narrowing of the retropalatal space, or in whom UPPP techniques failed but who refused maxillofacial advancement, may be included. On the other hand, patients with velopharyngeal failure, a pharyngeal swallowing disorder, or who had previously undergone palatal surgery, should be excluded. Finally, the results may be inadequate in patients with macroglossia, because the anterior traction of the palate may obstruct this respiratory airway.

The surgical technique is performed under general anesthesia with the patient in the Rose position. Local infiltration with 1% xylocaine with 1:100,000 epinephrine is performed at the level of the greater palatine foramen, the hard-soft palate junction, and the planned incision sites before the procedure for hemostasis.

In some patients, it may be necessary to remove any hypertrophic tonsils or the uvula beforehand. Next, a palatal incision is begun at the central hard palate posterior to the alveolus (approximately 2 cm anterior to the posterior border)

and is continued posteriorly, in a curvilinear fashion immediately medial to the greater palatine foramen. The tip or cephalic end of the flap should lie at least 1 cm proximal to the margin of the bone removal. The mucoperiosteal palatal flap is elevated, starting in the midline where the mucosa is thin. Laterally, the fibro-adipose tissue can be incised bluntly in order to elevate the flap. In this way, the palatine vessels are preserved. Elevation continues posteriorly along the hard palate and in a plane superficial to the tensor aponeurosis. The mucosal flap is elevated to expose 5-8 mm of tensor aponeurosis. This provides adequate tissue to grasp subsequent sutures but avoids excessive devascularization of the flap. Electrocautery is used to separate the hard and soft palates and to expose the nasopharynx. An 8-10 mm portion of the hard palate is removed using a Kerrison rongeur or drill. This includes the central palate exposing the posterior nasal septum; care must be taken to avoid damaging the inferior turbinates and lateral nasopharyngeal walls. Occasional bleeding is controlled with suction electrocautery. Palatal burr holes are placed at a 45° angle to the palate, extending from the oral surface of the palate into the nasal cavity. A tapered free needle is then used to pass a double suture through the drill holes into the nasopharynx. The suture is grasped in the nasopharynx and is withdrawn from the mouth. Care must be taken not to place any rotating force on the needles, in order to prevent fracture of the palatal bone. Sutures are then secured medially and laterally in the tensor aponeurosis. The soft palate is mobilized using steady anterior traction with a finger or blunt instrument behind the palate. The sutures are tied while the palate is retracted anteriorly; redundant mucosa may or may not need to be trimmed, and a tension-free closure is performed with fine absorbable sutures. A regular diet can commence on the first day. In one series,[15] transpalatal advancement pharyngoplasty produced a 67% response rate (defined as respiratory disturbance index (RDI) of less than 20 events/hour). Transient symptoms of mild nasopharyngeal reflux, similar to those experienced with UPPP, may occur; all patients undergo spontaneous resolution by six weeks. Partial palatal flap necrosis, orinasal fistula, and serous otitis media are infrequent but potential risks.

It should be borne in mind that transpalatal advancement is only part of the surgical treatment of OSAS. Treatment must include all segments of the complete upper airway. All segments of the airway, nasal, palatal, tongue base and hypopharyngeal spaces must be maximized if surgery is to be effective.

## Conclusions

Reports in the literature reveal that candidates who are subjected to concomitant UPPP surgery, hyoid myotomy, and tongue advancement show improvement rates of 85%, as seen by a decrease of RDI, AI, or AHI of at least 50%.[3] Complications or possible sequelae with this surgery are essentially the potential risk of acute upper airway obstruction and hemorrhage. After all, in itself,

UPPP presents risks of a velopharyngeal insufficiency and nasopharyngeal stenosis. However, we should always bear in mind that the greatest risk in genioglossal advancement is mandible fracture, although other complications have been reported,[16] such as dental injury, dehiscence of incision, hypo-esthesia, extrusion of screws, etc. Nevertheless, multi-layer surgery has now found its place in the treatment of moderate or severe OSAS, and in expert hands, remains a valid, effective, and safe surgical procedure. Surgeons performing palatopharyngeal surgery for the treatment of obstructive sleep disorders are required to have a sophisticated knowledge of the anatomy and physiology of the velopharyngeal complex, since the outcome and safety of surgery are contingent upon such knowledge.

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# UVULOPALATAL FLAP TECHNIQUE FOR THE TREATMENT OF OBSTRUCTIVE SLEEP APNEA SYNDROME

## Long-term results

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### Introduction

In 1980, one of the authors (GD) visited Dr Fujita in the USA, and learned his uvulopalatopharyngoplastic (UPPP) technique for the treatment of obstructive sleep apnea syndrome (OSAS). This was about a year before the technique was published in 1981.[1] GD was the first person in Norway, and probably in Europe as well, to use the Fujita UPPP technique for the treatment of OSAS. However, some risks were noted, for instance, pain, dysphagia, bleeding, infection, scarring, and altered palate function.[2] Loss of complete palatal closure may result in voice changes[3] and nasal regurgitation of fluid and food.[4] This problem is caused by excessive surgical removal of the palatal tissues and is termed velopharyngeal incompetence (VPI).[2] Shrinkage of the opening between the oro- and rhinopharynx has also been observed in some cases.

A cephalometric study of 20 normally sleeping persons and 20 patients with OSAS, demonstrated by polysomnography, was carried out and the data were compared.[5-7] The final result is illustrated in Figure 1. In OSAS patients, the soft palate was longer and thicker compared to normals. Also, the distance between the mandibular arch and the hyoid bone was larger, and the posterior airway space was long and narrow. In OSAS patients, the contact between the soft palate and the tongue was larger compared to normal sleeping subjects. Based on these cephalometric data, we developed a new flap technique.[7]

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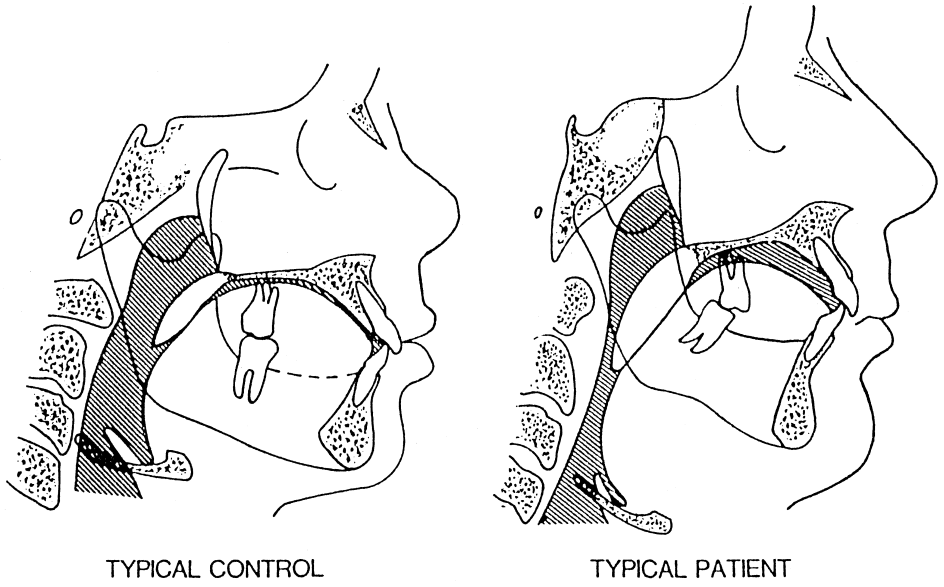


*Fig. 1.* Soft tissue profiles of a typical control and OSAS patient. Note especially the following characteristics of patient: decreased antero-posterior dimensions of the pharyngeal airway; increased length and thickness of the soft palate; inferiorly positioned hyoid bone.

## Method

The mucosa on the oral side of the uvula and the distal part of the soft palate is removed. The tip of the uvula is removed. As much as possible of the uvular muscle is maintained. A small incision is made in the anterior and posterior tonsil arches.

The distal part of the soft palate, together with the uvular muscle, is folded anteriorly and sutured (Fig. 2). We obtain a shorter soft palate, and a relatively large opening between the oro- and rhinopharynx, thus making it easier to breathe through the nose with the mouth closed. If the tonsils are present, bilateral tonsillectomy is carried out. Originally, general anesthesia and nasal intubation was used. Nowadays, local anesthesia and a $CO_2$ laser are used in many cases. More recently, in 1996, a modification of our flap technique was published by Powell *et al.*[2]

## Material and results

In the years 1983-1988, GD personally operated on 29 patients, who were able to attend follow-up examinations nine to 14 years postoperatively. In all cases, polysomnography was carried out pre- and postoperatively. Cephalometry was performed in 28 cases nine to 14 years after surgery. The material consisted of two females and 27 males. Their mean age was 51.1 years (range, 25-73 years).

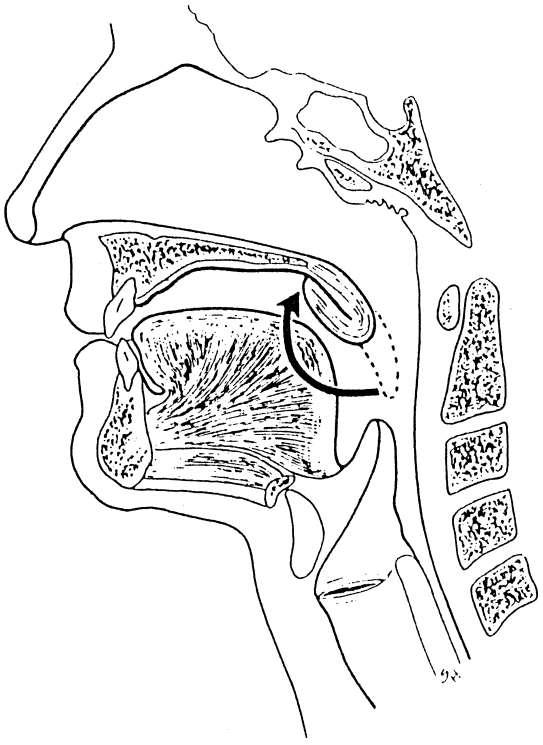

*Fig. 2.* The uvula and the distal part of the soft palate anteverted and sutured to the more cranially located part of the soft palate.

The mean body mass index (BMI) was 31.7 (range, 21.63-46.29). The majority of the patients were obese, with a BMI ranging from 25 to 45. The mean apnea-hypopnea index (AHI) was 58.41 (range, 20-122).

Using a visual analog scale (VAS) graded from 0 to 10 the following results were obtained (Figs. 3 and 4): snoring and apnea were considerably reduced, with 18 patients reporting no snoring and 19 no apnea; daytime sleepiness was also considerably reduced and was absent in 18 cases; oropharyngeal dryness was also reduced in some cases. This suggests that, nine to 14 years postoperatively, more patients are able to breathe through the nose with the mouth closed.

Side-effects, such as nasalation, regurgitation and swallowing problems, were not observed. Slight irritation in the throat was seen in eight of 29 cases. Consequently, no velopharyngeal incompetence was observed, which is found relatively often using the standard UPPP technique. Subjectively evaluated, the results seen nine to 14 years after surgery are as follows: satisfied patients: 26/29 (89.65%); dissatisfied patients: 3/29 (10.35%); the three dissatisfied persons are now using continuous positive airway pressure (CPAP).

The final results for the entire group are shown in Table 1. The mean BMI is approximately the same pre- and postoperatively; the range is also about the

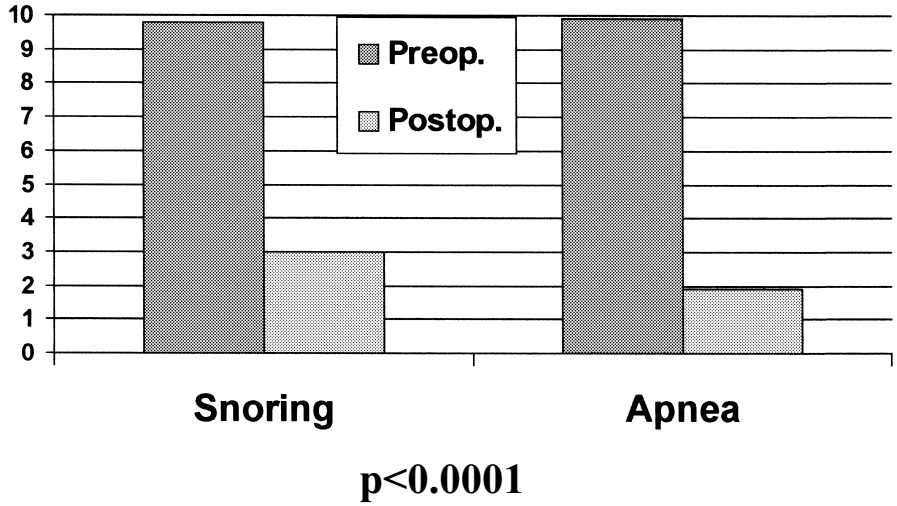


*Fig. 3.* Visual analog scale pre- and postoperatively (n=29).

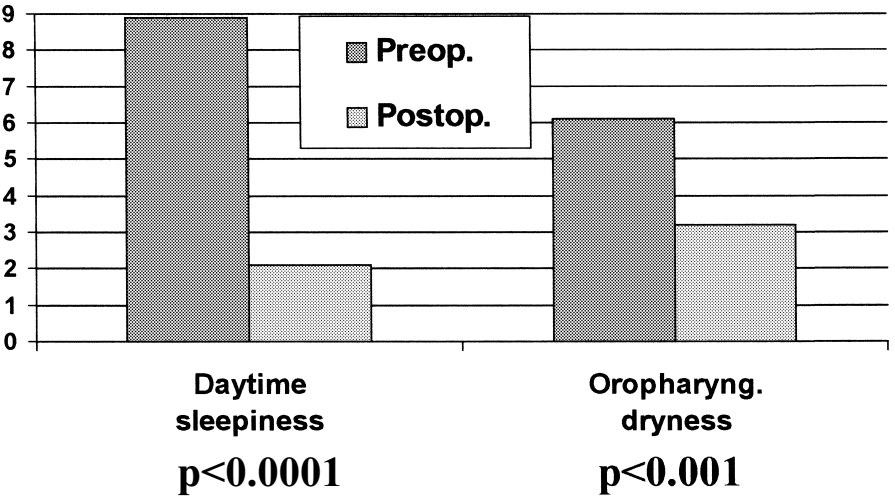


*Fig. 4.* Visual analog scale pre- and postoperatively (n=29).

same. The mean postoperative AHI was 31.5; range, 1-100. This value was reduced compared to the mean preoperative value of 58.4, range, 20-122.

Polysomnography was carried out preoperatively and nine to 14 years after surgery in all cases. If 'responders' are defined as those having an AHI reduction of 50% or more, 19 of 29 (55.2%) can be classified as responders. Six patients (Group A) had a postoperative AHI of >10, ten patients (Group B) had a postoperative AHI of <10. This is in agreement with findings from other studies.[8-14]. However, there may be a difference in the patient populations. Our material includes many severely obese patients who later were shown not to be the best candidates for surgery. The pre- and postoperative AHIs and BMIs of

*Table 1.* Results preoperatively and nine to 14 years postoperatively (two females, 27 males)

| | *Mean* | *Range* |
|---|---|---|
| Preoperative BMI | 31.7 | 21.6-46.2 |
| Postoperative BMI | 30.2 | 21.7-44.1 |
| Preoperative AHI | 58.4 | 20-122 |
| Postoperative AHI | 31.5 | 1-100 |

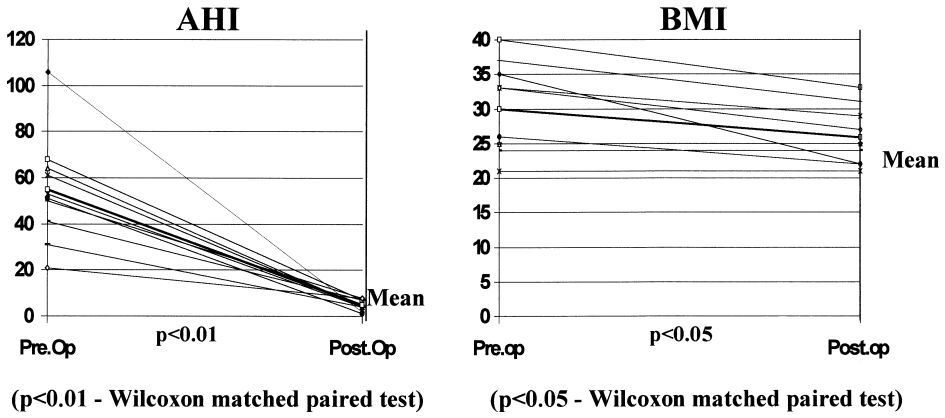


*Fig. 5.* AHI and BMI in responders Group B (responders Group B: postoperative AHI <10, reduction in AHI of 50% or more).

ten patients with a postoperative AHI of <10 are shown in Figure 5. Preoperatively, the AHI was between 20 and 106. The mean reduction in AHI and BMI was statistically significant. Five of these ten patients had a normal or almost normal BMI pre- and postoperatively. In the remaining five obese patients, the BMI was reduced postoperatively.

The pre- and postoperative AHIs and BMIs of the remaining 19 patients are shown in Figure 6. Six of these patients had a reduction in AHI of 50% or more (Group A). These are classified as responders. If we remove the six responders, there is no statistically significant change in mean value between pre- and postoperative AHI and BMI.

Six months after surgery, polysomnography was carried out in the six patients who showed an AHI reduction of 50% or more (responders Group A; Fig. 7). At that time, the body weight was reduced in all cases, and AHI was found to be <10. Later on, the body weight increased, and nine to 14 years after surgery, AHI was found to be between 12 and 68. This finding indicates that postoperative BMI is an important factor influencing the outcome of surgical treatment.

Cephalometric examination was carried out nine to 14 years after surgery in 28 patients, ten with a postoperative AHI of <10 (responders Group 2) and 18 with an AHI of >10 (Group 1). The data were compared. In the responders

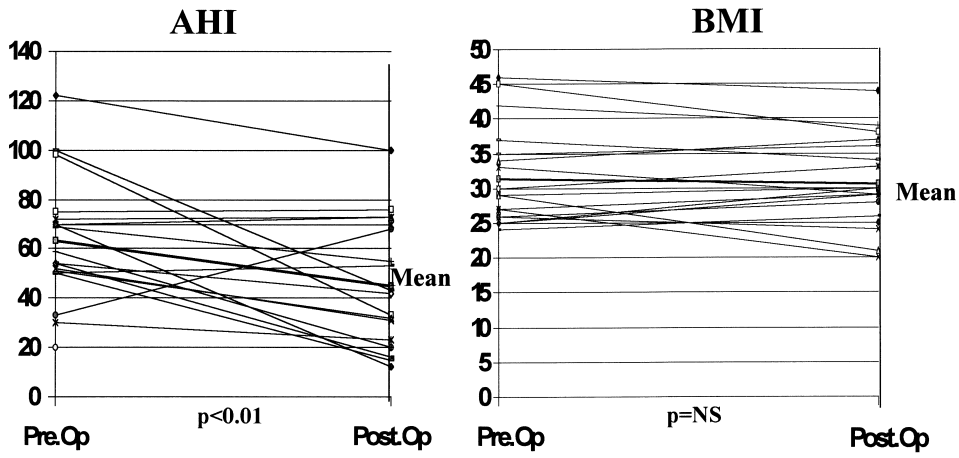


*Fig. 6.* AHI and BMI in 19 patients with postoperative AHI of >10 (non-responders + responders Group A). Wilcoxon matched paired test.

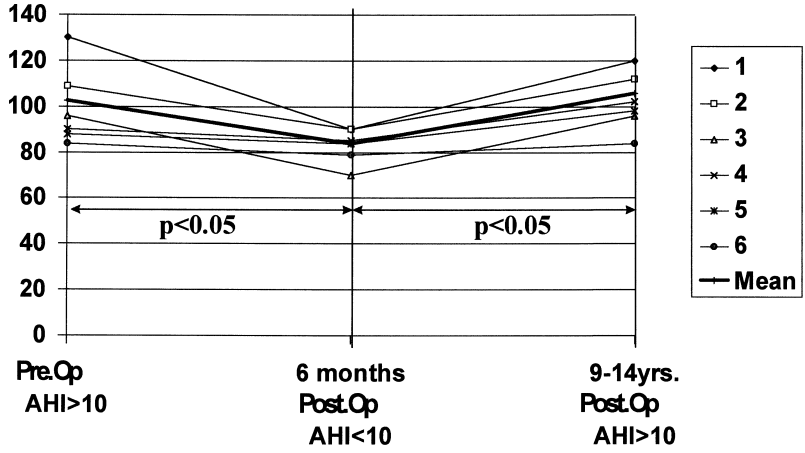


*Fig. 7.* Effect of body weight in responders Group A (responders Group A: AHI reduction of 50% or more and AHI of >10). Wilcoxon matched puired test.

Group 2 we found: *a.* the length of the tongue was shorter (Table 2); *b.* the vertical distance to the sella point was shorter; *c.* the distance between the hyoid bone and the mandibular arch was shorter (Table 3); *d.* the posterior airway space was larger (Table 4). The differences between the two groups were statistically significant. This finding indicates that, in the responders Group 2, the upper airways are more open postoperatively. It also indicates that, preoperatively, these patients had an obstruction usually located in the soft palate region. After surgery, this obstruction was removed. Preoperatively, five of the ten responders were obese, and it may be that BMI reduction has contributed to opening up the upper airways. The remaining 19 patients with AHIs of >10

*Table 2.* Tongue length (V-T) mm, nine to 14 years after surgery (*n*=28)

| | | |
|---|---|---|
| Group 1 | (n=18, AHI ≥10) x = 87.0 | SD 5.7 |
| Group 2 | (n=10, AHI <10) x = 79.2 | SD 9.7 |
| Difference | $\bar{x}$ = 7.8 $p$<0.01 | |

*Table 3.* Vertical position of the hyoid bone (AH⊥S, AH⊥ML) mm, nine to 14 years after surgery (*n*=28)

| | | | |
|---|---|---|---|
| AH⊥S | | | |
| | Group 1 | (n=10, AHI <10) $\bar{x}$ = 118.3 | SD 12.6 |
| | Group 2 | (n=18, AHI ≥10) $\bar{x}$ = 103.3 | SD 7.0 |
| | Difference | $\bar{x}$ = 15 $p$<0.01 | |
| AH⊥ML | | | |
| | Group 1 | (n=18, AHI ≥10) $\bar{x}$ = 30.6 | SD 5.6 |
| | Group 2 | (n=10, AHI <10) $\bar{x}$ = 20.7 | SD 8.8 |
| | Difference | $\bar{x}$ = 9.9 $p$<0.001 | |

*Table 4.* Lower pharyngeal airway space (V-LPW) mm, nine to 14 years after UPPP (*n*=28)

| | | |
|---|---|---|
| Group 1 | (n=18, AHI ≥10) $\bar{x}$ = 13.5 | SD 6.5 |
| Group 2 | (n=10, AHI <10) $\bar{x}$ = 16.2 | SD 6.6 |
| Difference | $\bar{x}$ = 2.7 $p$<0.01 | |

nine to 14 years after surgery, may have obstructions located in the lower part of the upper airways.

## Comments and conclusions

Subjective evaluation showed that 26/29 patients (89.6%) were satisfied with the result of the operation. The snoring, apnea and daytime sleepiness were considerably reduced. As in other studies, the improvement of most symptoms was unrelated to the degree of improvement in AHI.[8,10] In a study of simulated driving performances, Haraldsson *et al.*[15,16] found an improvement in performance after UPPP in patients in whom the procedure had significantly reduced the number of apneas, and in subjects in whom there was little effect on AHI. This indicates that even partial improvement of upper airway resistance may have a positive effect on the quality of sleep, and as a result improve daytime alertness. This is in accordance with the results of the present investigation in which 89.6% were satisfied with the result of the operation.

Polysomnography nine to 14 years after surgery showed that 16 of 29 patients (55.2%) were classified as responders. Approximately the same percentage was found in other studies.[4,5,8-14] The reason for the difference between the

subjective evaluation of the results and the objective data found by polysomnography is unknown. When the present study was started in 1983, we had to select many obese patients with a high BMI. It may be that the results of the present investigation would have been better if patients with a normal BMI and a lower AHI had been selected.

Cephalometry nine to 14 years after surgery in ten patients with an AHI of <10 showed that the oropharyngeal dimensions were larger compared to data from 18 other patients. This indicates that the main preoperative obstruction was located in the soft palate region, and that this obstruction was removed by surgery. BMI reduction in five obese patients may also have contributed to opening up the upper airways. Obstructions located in the lower part of the upper airways were probably present in the remaining 19 patients. In six responders, six months after the operation, BMI was normalized, and polysomnography at that time showed an AHI of <10. Later on the body weight of these patients increased, and at the present time they have an AHI of between 12 and 46. This finding indicates that, in obese patients with OSAS, postoperative BMI reduction is essential for the successful outcome of surgical treatment. This has also been noted in other studies.[17-23]

Preoperatively it is difficult to normalize the BMI in obese patient with OSAS. Treatment with CPAP or tracheostomy has been tried, together with a strict diet regime. A postoperative diet regime and many follow-up visits are also important in order to reduce BMI and maintain it at a normal level.

The flap technique has some advantages compared to the standard UPPP technique. No serious side-effects or velopharyngeal incompetence were observed.

It is difficult to say whether the flap technique gives better long-term results compared to the standard UPPP technique, because the present study contains obese persons with a high AHI and BMI. Consequently, it is not possible to compare these results with those obtained with the standard UPPP technique on subjects with a lower AHI and BMI.

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# LONG-TERM FOLLOW-UP OF OBSTRUCTIVE SLEEP APNEA SYNDROME FOLLOWING SURGERY IN CHILDREN AND ADULTS

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## Introduction

Obstructive sleep apnea syndrome (OSAS) is a life-threatening disorder with cardiovascular complications, which may lead to sudden death during sleep.[1] The modern treatment of OSAS includes drug therapy, nasal continuous positive airway pressure (CPAP), several kinds of upper airway surgery such as tonsillectomy, adenoidectomy, uvulopalatopharygoplasty (UPPP), and midline glossectomy. Several reports concerning the long-term results of surgical procedures on breathing during sleep and sleep quality have been published. For children, tonsillectomy and adenoidectomy are the most commonly recommended treatment.[2] However, adult patients with OSAS tended to respond poorly to surgical treatment.[3-11] The success rate of surgical procedures has been reported to be between 50 and 70%. He *et al.*[12] demonstrated that the cumulative survival of a group of patients treated with UPPP alone was not different from that of untreated patients with an apnea index of >20. Patients with severe OSAS can be treated effectively with nasal CPAP. A recent randomized controlled study of nasal CPAP provided confirmative evidence of the clinical effectiveness of OSAS.[13] However, many patients refuse CPAP and prefer surgery to enlarge the upper airway, because of its potential as a long-term essential cure. The compliance of CPAP is reported to be 40~60%.[14,15] It is still controversial whether surgery, especially in adult patients with OSAS, offers reliable and long-term benefits. The present study describes the long-term results after surgical procedures for OSAS in 20 children and 17 adults.

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## Patients and methods

From February 1986 to August 1996, 53 consecutive patients with OSAS underwent surgical treatment. A diagnosis of OSAS was made in patients with an apnea index (AI) greater than 10, oxygen desaturation associated with respiratory events, and/or symptoms such as excessive daytime sleepiness and morning headache, etc. The surgical modality was determined by the Müller method, cephalometry, and measurements of the pressure of mesopharynx and esopharynx during sleep, which provided the localization of the airway collapse.

Thirty-seven of the 53 patients completed the questionnaire. These consisted of 27 males and ten females with a mean age of 23 years (range, 1-61 years). There were 20 children (<15 years) and 17 adults. The surgery included UPPP, tonsillectomy, adenoidectomy, laser midline glossectomy, and inferior turbinectomy. The duration of follow-up averaged 92 months (range, 37-150 months). The questionnaire included the present height and body weight of the patient, presence or absence of snoring, of sleep apnea, of daytime sleepiness, and of late postoperative complications, and subjective outcome of surgery. Late postoperative sleep studies measured by a portable apnomonitor at home were obtained in six patients.

Questionnaire and AI data were analyzed by the Student *t* test. A probability value of $<0.05$ was considered statistically significant.

## Results

A significant increase in body mass index (BMI) at the time of the questionnaire compared with that before surgery was observed in children, which was due to normal growth with age. On the other hand, no significant difference was seen in the adults.

The changes in snoring were evaluated by the patients' bed partners. All the children showed an absence or marked decrease of snoring after surgery. Although most of the adult patients showed an improvement of snoring, four were found to be unchanged. However, these four patients replied that snoring did improve immediately after operation compared with preoperatively, but that it became worse with time. This finding suggests that all patients can be defined as responders immediately after surgery.

The outcome of apnea symptoms was examined. Similarly to snoring, sleep apnea totally disappeared in children. In adults, four patients showed no change in sleep apnea in the late postoperative period, two of whom had shown a transient improvement immediately after surgery.

The symptomatic response of daytime sleepiness was analyzed. Complete elimination was observed in 16 patients, and a moderate improvement in four children. In adults, daytime sleepiness disappeared in eight patients, and four

showed a moderate improvement, but one patient complained of daytime sleepiness. This was the same patient with unchanged snoring and sleep apnea.

There were two children and eight adults with late complications. The two children complained of rhinolalia. In adults, six patients complained of some nasal regurgitation due to velopharyngeal incompetence, and two felt an unpleasantness in the throat.

Based on symptomatic success and the presence of complications, the surgical outcome was evaluated by the questionnaires. All children except one showed a satisfactory outcome after surgery. One patient who had undergone surgery during childhood had no opinion concerning the outcome, despite the absence of snoring, sleep apnea and postoperative complications. Of the adults, four complained of an unsatisfactory outcome and one had no opinion.

Eleven of the 20 children underwent a preoperative sleep study, in whom the mean AI was 14 per hour. A sleep study was performed in only two patients in the early postoperative period. The AI returned to the normal range in both patients. All the adult patients underwent a sleep study before the operation, and their mean AI was 40. Immediately after operation, the AI was significantly decreased to 4 ($n = 8$), and remained within a normal range in the late postoperative period ($n = 6$). However, we could only obtain a long-term result on the sleep study in one of the four patients with an unsatisfactory outcome. The AI of this patient changed from 51 preoperatively to 16 in the late postoperative period.

## Discussion

The gold standard for the treatment of OSAS in infants and children is tonsillectomy and/or adenoidectomy.[2] Although associated problems such as an abnormally long soft palate, retroposition of the mandible, or soft tissue infiltration behind the base of the tongue, can occur after operation, none of our patients experienced residual problems after operation. It has also been reported that OSAS may recur after puberty, especially in males.[16] However, no apparent recurrence of sleep-related symptoms in our child patients was observed, despite the increased BMI. Although one patient did not reply to the question on surgical outcome, the symptomatic improvement without late postoperative complications suggests that surgery was successful in this patient. Thus, these findings confirm that tonsillectomy and/or adenoidectomy for infants and children with OSAS should be the first mode of treatment.

Analysis of the surgical success or failure of UPPP in adult patients with OSAS involves several different aspects. The long-term results of surgery on breathing during sleep, and on sleep quality, have been extensively investigated. Conway *et al.*[7] concluded that, after one year of follow-up, 20 of 33 patients could be defined as responders. However, weight gain after surgery jeopardized the good surgical results. Guilleminault and coworkers[4] reported

that weight increase after surgery was also associated with poor objective results. In the present study, there was no significant difference between pre- and postoperative average BMI. Moreover, patients with unsatisfactory symptomatic results showed no significant changes in BMI. Various reports have indicated a discrepancy between subjective improvement and the absence of objective favorable changes.[8-10] In other words, the results obtained by questionnaire tend to be better in most patients after UPPP, irrespective of the poor results of postsurgical sleep monitoring. Although about half the adult patients underwent postoperative sleep studies immediately and well after surgery, AI returned to the normal range in all patients examined. In our patients, the postsurgical signs showed good consistency with the subjective improvement, which would suggest appropriate preoperative assessment of the localization of the airway obstruction. We could only obtain the AI in one patient with an unsatisfactory symptomatic outcome, in whom this had declined from 51 to 16 after UPPP. The other three patients with unsatisfactory subjective outcomes could be expected to have poor objective results. The possibility of weight gain after surgery can be dismissed as a cause of the poor subjective results, because there was no change in BMI. Another possible causative factor of the failure of late postoperative improvement in adult non-responders, is inadequate selection of the surgical procedure due to insufficient assessment of the localization of the obstruction in the airway.[17,18] Recently, we introduced dynamic magnetic resonance imaging (MRI) during awake and asleep conditions in order to assess airway collapse.[19] Lastly, airway collapse of unknown origin could have occurred, presumably due to the local deposit of flaccid tissue in the collapsible part of the airways. A combination of surgical options and nasal CPAP may be effective in these patients.

In conclusion, the long-term follow-up of OSAS after surgery, including a questionnaire and a sleep study, was performed in order to evaluate the effectiveness of surgery for OSAS. Tonsillectomy and/or adenoidectomy were proved to be quite effective in children with OSAS. Approximately 80% of adults with OSAS showed satisfactory results after UPPP plus tonsillectomy. The current strategy for improving the success rate of the surgical treatment for OSAS is to localize the obstruction in the airway preoperatively, by use of the Müller maneuver, continuous pressure measurement of the upper airway, and dynamic MRI.

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# CONGENITAL CRANIOFACIAL MALFORMATIONS AND OBSTRUCTIVE SLEEP APNEA SYNDROME

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## Introduction

Numerous craniofacial malformations may be responsible for upper airway obstruction, and, in particular, for apnea of varying severity. The mechanisms of action involved also vary considerably, even if they all converge into a single pathological condition: reduction of the rhinopharyngeal air space.

Regardless of brain malformations that can give rise to the central type of respiratory disorders, the reduction of the rhinopharyngeal air space may occur either due to the anomalous presence of brain tissue, or on account of skeletofacial malformations. In the latter event, retrusion of the maxilla or of the entire facial complex (Figs. 1 and 2) results in a decrease in the space for the air flow which, via the nasal fossa, should reach the rhinopharyngeal cavity and then the trachea. In these cases, the soft palate and its musculature are positioned at the rear and are probably sucked back into the hypopharynx, or cause obstruction of the hypopharyngeal space, of varying severity, during air intake (Figs. 3, 4). Even a poorly developed mandible may be positioned at the rear and may contribute to creating the conditions for reducing the hypopharyngeal air space (Fig. 5). In turn, retroposition of the mandible determines that the position of the normal hyoid bone is lower and more to the rear, and therefore, the entire connected muscular ring fails to retain the correct tension, particularly during sleep, thus favoring episodes of apnea. Moreover, the volume of the oral cavity is reduced in the presence of a small mandible, thus resulting in disproportion between the tongue and the oral cavity. Again, this results in hypopharyngeal airway obstruction, especially during sleep.

An exact description of the pathophysiological mechanisms will be found in the specific chapter; however, it is worthwhile mentioning here that experimental and clinical studies have demonstrated that the origin of pharyngeal obstruction lies in the imbalance between the negative pressure exerted by the

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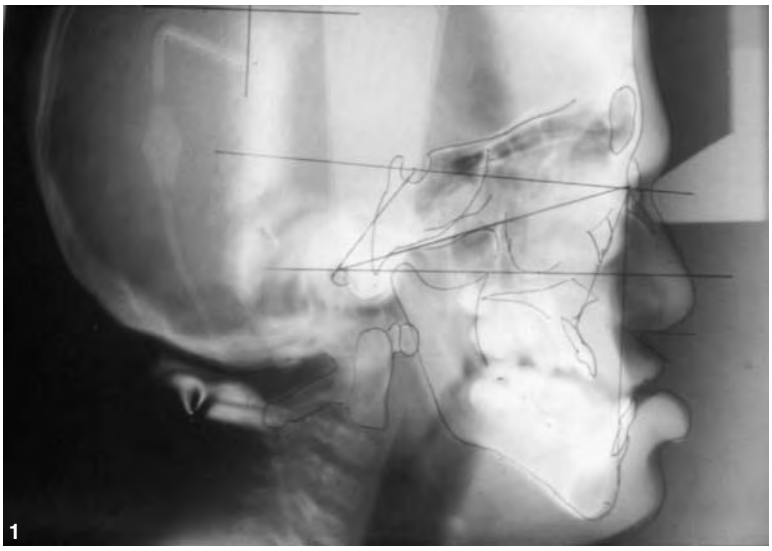

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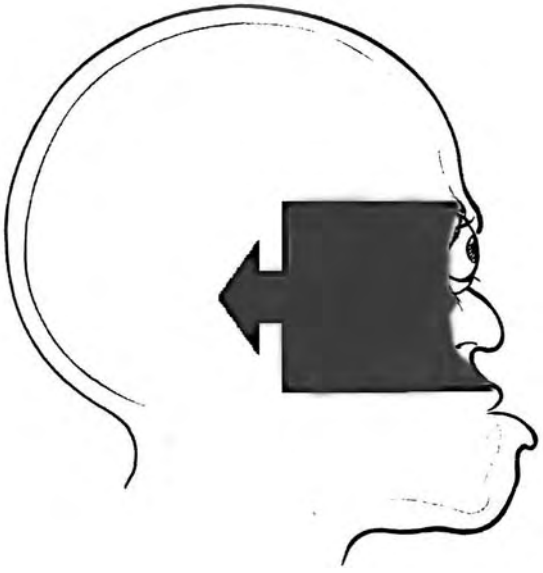

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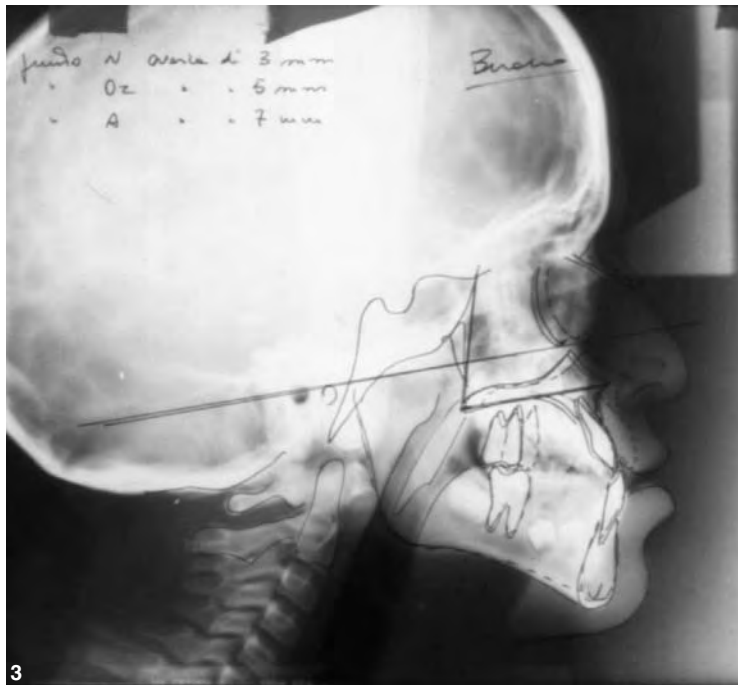
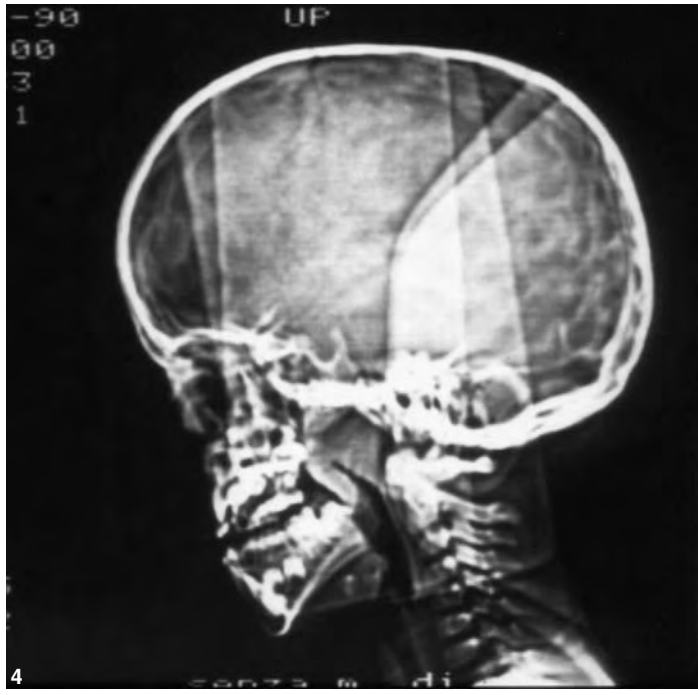
*Figs. 1 and 2.* Retrusion of the middle third of the facial skeleton.

activity of the diaphragm and inspiratory muscles, and the collapse of the upper airway muscles.[1-4] During REM sleep, the muscles of the upper airway, tongue and velopharyngeal sphincter, unlike the diaphragm muscles, are less active; this situation results in the onset of the obstruction, and of the collapse responsible for the episodes of apnea. During these apnea crises, there is a progressive decrease in the arterial saturation of oxygen ($paO_2$), and an increase in the arterial pressure of $CO_2$ ($paCO_2$); furthermore, changes in cardiovascular function (arrhythmia, hypertension, etc.) may also occur. At the end




*Figs. 3 and 4.* Retrusion of the soft palate.

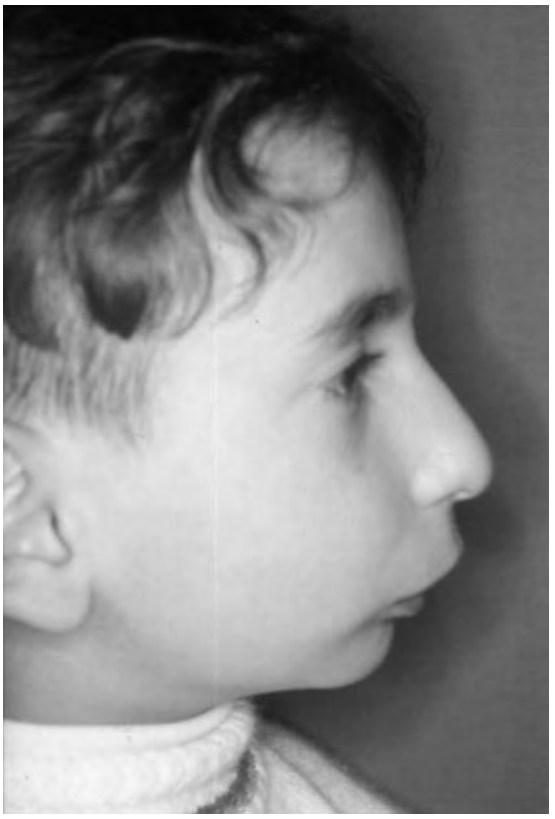


*Fig. 5.* Patient affected by Pierre Robin syndrome. Evident sagittal hypodevelopment of the mandible.

of the apneic crisis, hypoxia and hypercapnia not only cause the patient to wake up, but, at the same time, result in contractions of the muscles at the level of the limbs and of the mouth and chin, thus re-establishing patency of the upper airways. This causes irregularity in the patient's sleep, as well as interruption of his night rest.

## Classification

The malformations which may lead to obstructive sleep apnea syndrome (OSAS) can be either congenital or acquired. Congenital craniofacial malformations comprise a very heterogeneous group. These result from errors in development during embryonal and fetal life, and it has been revealed that the earlier the error becomes manifest, the more severe the malformation will be.

The etiology still remains to be fully elucidated, but, in most cases, is related to occasional factors; however, some risk factors have also been identified,

such as infections occurring during pregnancy (HIV, cytomegalovirus, toxoplasmosis, measles, virosis, etc.), metabolic disorders such as diabetes, the use of medicines and drugs, radiation.

Furthermore, the pathogenic mechanisms are not yet fully understood, and are not always easily detectable, since they are often present, at the same time, in the same syndrome. This explains the numerous clinical patterns and the difficulty in producing a universally acceptable classification.

As far as the craniofacial malformations correlated with OSAS patterns are concerned, for convenience, these can be divided into the following groups:

*Malformations of the central nervous system*

These are able to determine poor functioning of the automatic mechanisms of lung ventilation: for example, malformation of the brainstem and cerebellum (Arnold-Chiari deformity) or malformation of the cerebellum itself (Dandy-Walker syndrome), or, again, some typical forms of primary megacephaly, such as Soto's syndrome. The mechanisms specifically responsible for the onset of central apnea are: *(1)* absence of respiratory impulse and of muscular activity; *(2)* ventilatory instability, onset of which may occur during periodic respiration; *(3)* temporary inhibition of the respiratory impulse.

*Anatomical alterations peculiar to the pharynx*

The volume of the rhinopharyngeal space may be considerably reduced for various reasons. The anatomical situations that can determine a reduction in

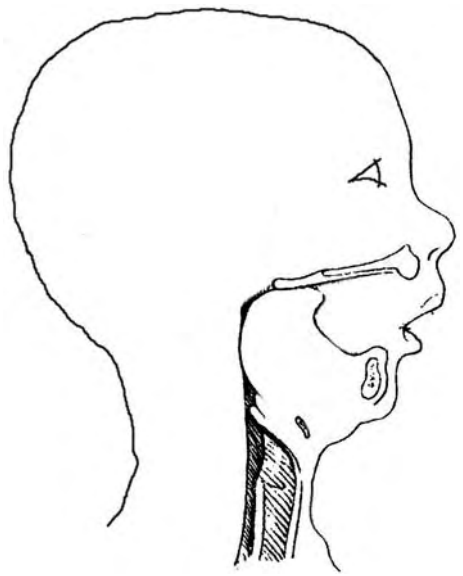
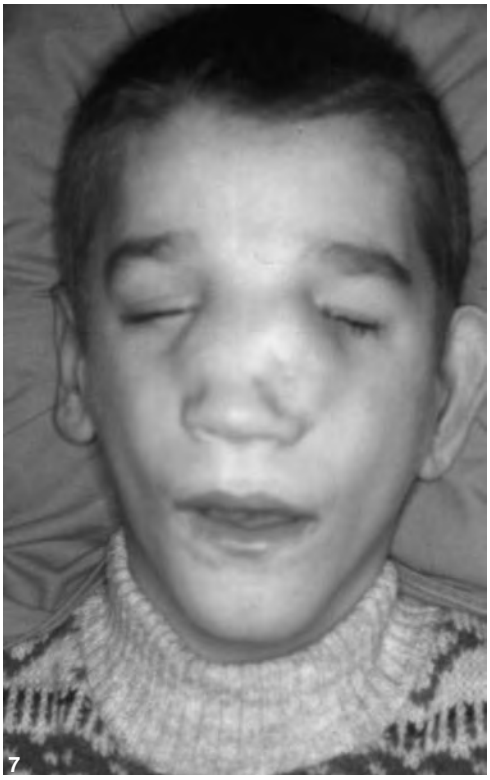
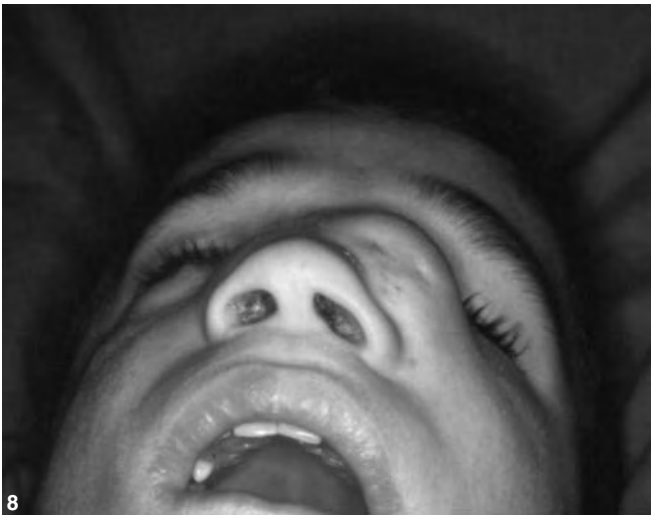


*Fig. 6.* Diagram of glossoptosis in a patient with a hypoplastic mandible.





*Figs. 7 and 8.* Patient affected by a nasopharyngeal encephalocele.

the pharyngeal air space are macroglossia, glossoptosis (Fig. 6), hypertrophy of the tonsils and/or adenoids, soft palate deformities, velopharyngeal dysfunctions, and choanal atresia. Some of these conditions may be associated with, or caused by, reduction of the oral cavity volume (microgenia, macrognatia) (Figs. 1 and 5). Obesity may also be considered a cause of a reduction in the rhinopharyngeal space, since it would be responsible for the accumulation of adipose tissue in the laterocervical areas and in the thickness of the pharyngeal walls.

*Cephaloceles*

These are a particular congenital brain malformation which involve the nasal fossa or the pharyngeal space through a defect in the cranial base and the dura mater, usually situated along the median line. Cephaloceles are classified into various forms according to the contents of the hernial sac. The most common are: *(1)* meningocele, comprising only a meningeal wall containing liquor; *(2)* meningoencephalocele or encephalocele, formed by a meningeal wall containing brain tissue and liquor (Figs. 7-9); and *(3)* meningoencephalocystocele, in which the herniation of the ventricular system is associated with the previous form. The cephaloceles that can determine a real OSAS pattern are the nasopharyngeal encephaloceles, *i.e.*, those prolapsing in the rhinopharyngeal cavity due to interruption of the ethmoid and/or of the sphenoid bone. The nasopharyngeal encephaloceles are classified into: transethmoidal, sphenoethmoidal and sphenonasopharyngeal. The mode of onset of an OSAS pattern and its severity are directly related to the extent to which the encephalocele fills the pharyngeal space (Fig. 10).

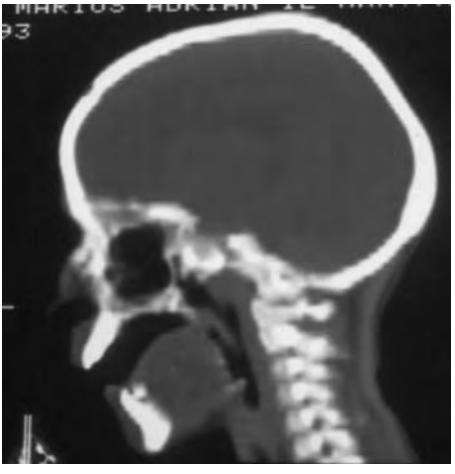


*Fig. 9.* CT of an encephalocele involving the nasal fossa.

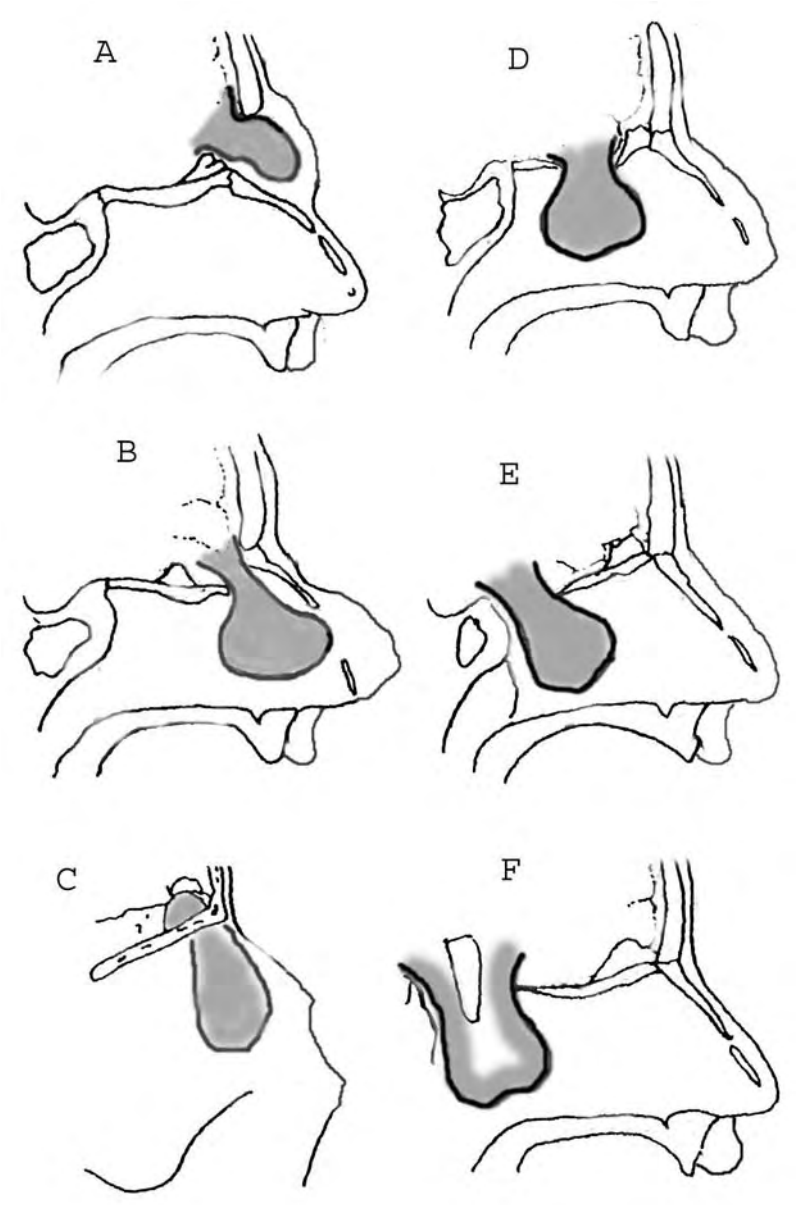
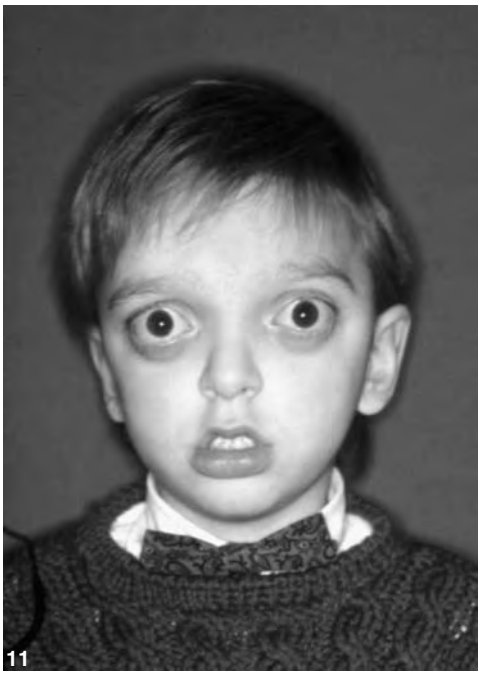
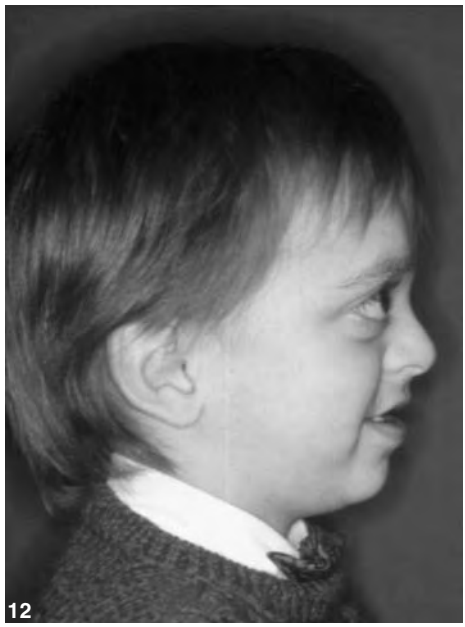


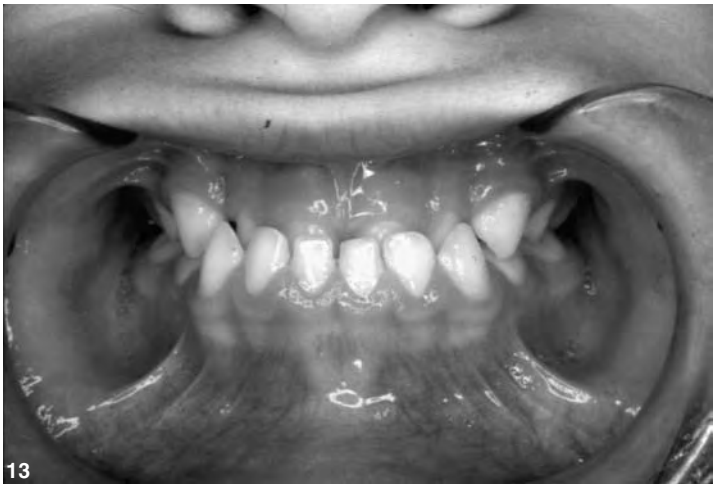

*Fig. 10.* Diagrams of the various types of nasopharyngeal encephaloceles.

### *Craniofacial stenosis or craniofacial dysostosis*

Craniofacial stenosis has been studied with particular attention by Cohen,[5] who, in 1975, listed 37 different types, amongst which the most common, and, therefore, the better known, are: 'kleeblattschädel' anomaly (triphyllocephalia); Crouzon's syndrome; Apert's syndrome; Pfeiffer's syndrome; Saethre-Choetzen's syn-

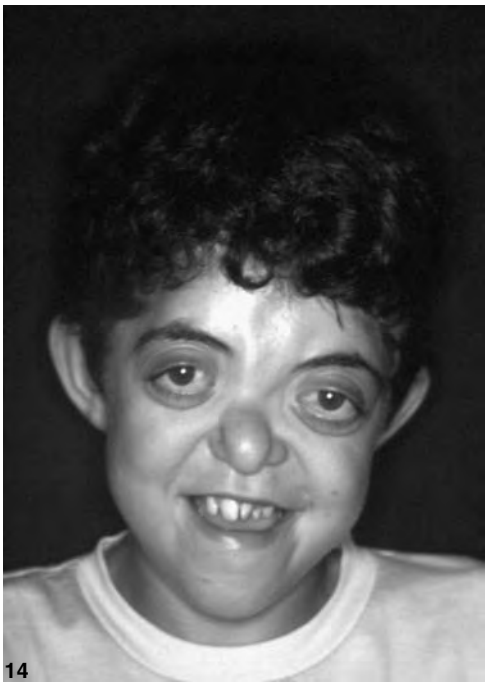


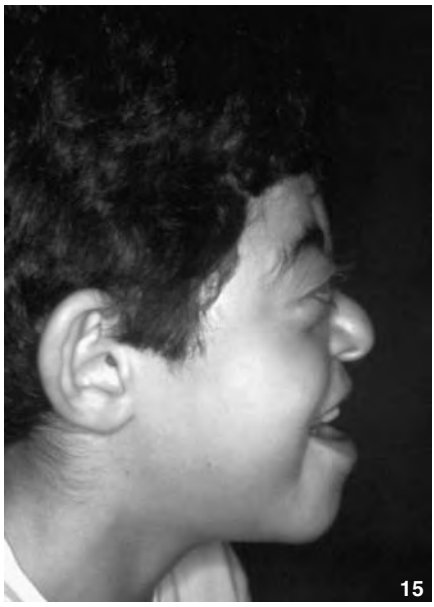



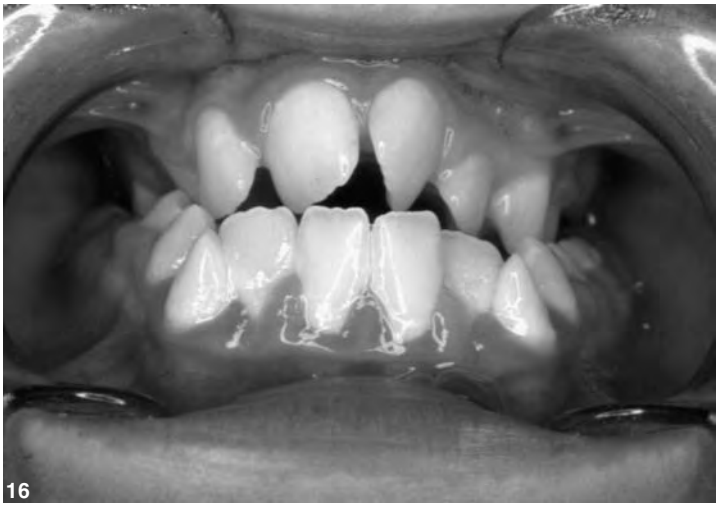




*Figs. 11-13.* Patient affected by Crouzon's syndrome: frontal, lateral, and occlusal views.

drome; and Carpentier's syndrome. Crouzon's syndrome (Figs. 11-13), Apert's syndrome (Figs. 14-16), Pfeiffer's syndrome and 'kleeblattschädel' anomaly are the ones most frequently responsible for OSAS. In fact, in these syndromes, the malformation results in underdevelopment of the volume, especially on the sagittal and vertical planes, of the middle third of the facial complex. From a pathogenic point of view, premature fusion of the cranial and center-facial sutures occurs, which leads to growth disorders involving the cranial bones and the orbital-zygomatic-maxillary complex.




*Figs. 14-16.* Patient affected by Apert's syndrome: frontal, lateral, and occlusal views.

There may be evidence of functional problems of a neurological kind, mainly due to intracranial hypertension, which if present and not promptly corrected, may give rise to hydrocephalus or to cerebral disorders or infections. Cases of mental retardation are rare in Crouzon's syndrome, whereas they are more frequent in Apert's syndrome. An exact evaluation of mental retardation, in these patients, is not easy since, in the past, they were rapidly isolated or hospital-

ized in special centers for mental disorders, as they were considered, on account of their physical aspect only, to be mentally retarded. Of course, this contributed to creating mental disorders even in mentally normal patients.

At a cranial level, early closure of the sutures leads to various craniostenosis conditions which are then associated with faciostenosis; this results in modifications in the cranial base with a reduction in anterior cranial base length and an increase in cranial base angle. Moreover, a reduction in anterior cranial base length, associated with hypoplasia of the upper jaw and of the zygoma, in turn results in a reduction of the orbital volume with relevant, more or less severe, exophthalmos. This condition is much more frequent in Crouzon's syndrome than in Apert's syndrome.

In both syndromes, excessive transversal development of the ethmoid may be observed with an increase in interorbital distance (hypertelorism) (Figs. 17 and 18), whereas only in Apert's syndrome an inclination towards the bottom of the zygoma is found, with a consequent anti-mongoloid inclination of the palpebral fissure.

At the level of the middle third of the face, retrusion of the maxilla, not always marked at birth, tends to become more marked during growth, due to the impossibility of extrusion of the teeth. At an occlusal level, third-class occlusion occurs with overbite, anterior open bite, and contraction of the transverse diameters of the upper arch.

A cleft in the secondary palate can be found in Apert's syndrome (Fig. 19). A distinct feature in the diagnosis of Apert's syndrome is syndactylia of both the hands and the feet (Figs. 20 and 21).

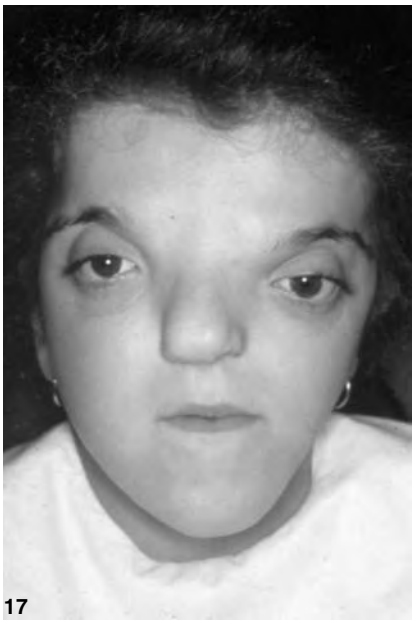
There are also important differences between the two syndromes, despite the many aspects common to both, which led Tessier[6] to coin the term 'Croupert syndrome', in order to underline the possibility that one syndrome may drift into the other (Fig. 22).

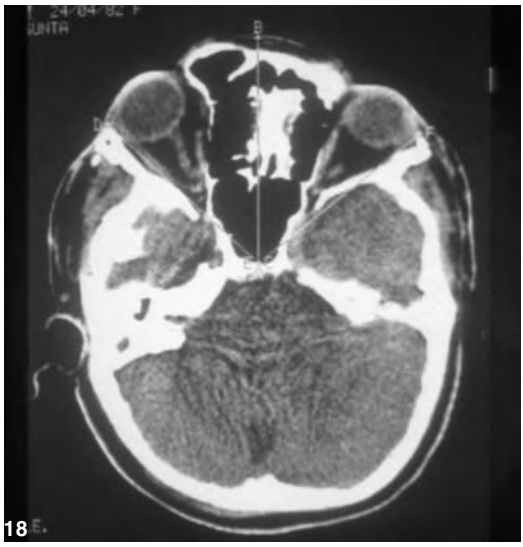
*Crouzon's syndrome*

Crouzon's syndrome is hereditary (Figs. 23-26), and has a dominant autosomal character with almost complete penetration. Coronal, sagittal, and lambdoid sutures may be involved. Mental retardation can be associated if a brain lesion or intracranial hypertension are present. The sphenoid bone is located lower down and, consequently, the junction between the anterior and the middle cranial fossa is below the normal level. The middle cranial fossa is more developed, both anteriorly and inferiorly.

Microrbitism is observed since both the antero-posterior and medio-lateral diameter of the orbits are markedly reduced; this results in a considerable reduction in the volume of the orbital cavity, into which the eyeball cannot fit. The orbits present a similar picture of deformity, albeit with some differences between the two sides due to the sutures involved. For this reason, the inclination of the palpebral rim is normal.

A cleft palate is rare, and the morphology of the limbs is normal. The upper





*Figs. 17 and 18.* Patient affected by hypertelorism and axial CT of the case.

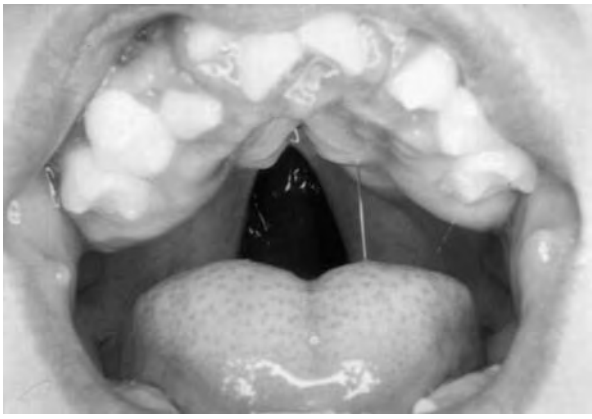
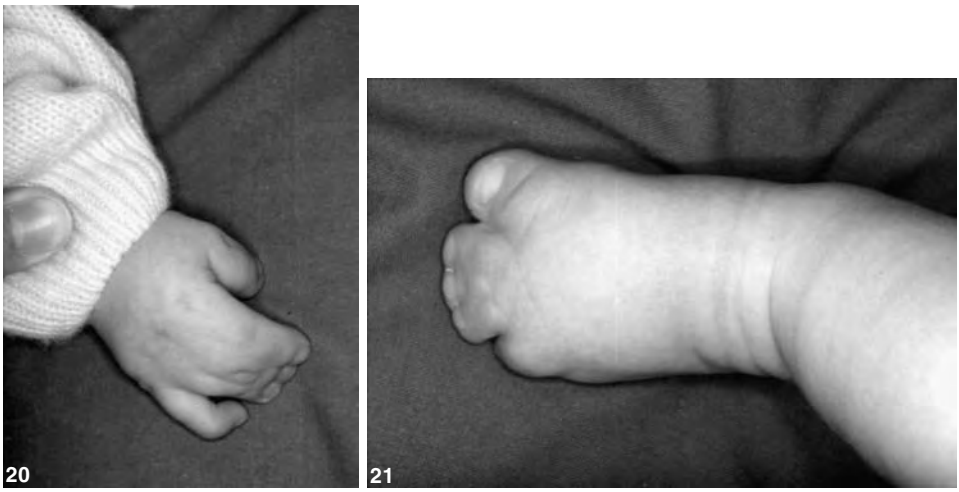


*Fig. 19.* Secondary palate cleft in a patient with Apert's syndrome.

jaw is markedly retropositioned, the deformity being proportional to the severity of the microrbitism, since this, in turn, is affected by the severity of the morphological disorder of the ethmoidal and sphenoidal bones. The severe change in dental occlusion is associated with anterior open bite, third occlusal class, and contraction of the palate. Retention of the permanent teeth, besides causing marked dental crowding, contributes towards decreasing the maxillary growth. These factors, associated with reduction in the development of the pterygo-




*Figs. 20 and 21.* Syndactylia of the second, third and fourth fingers in a patient with Apert's syndrome.

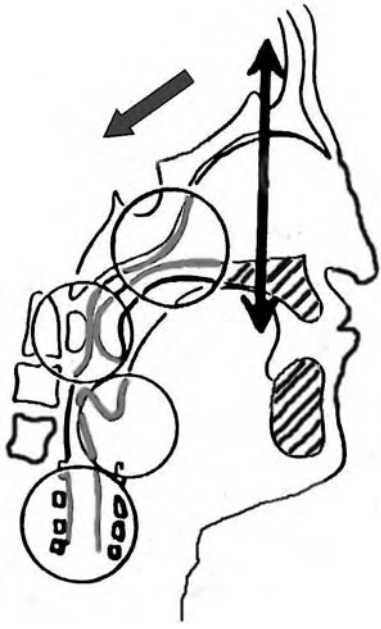
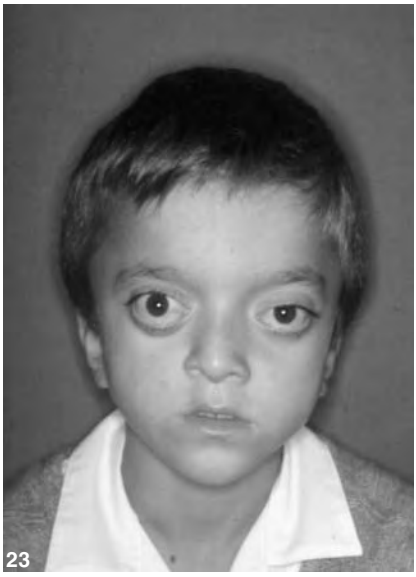


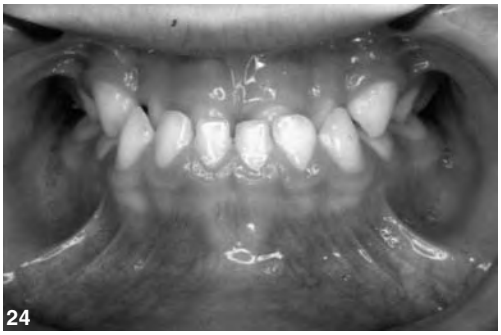
*Fig. 22.* Diagram of the defects characterizing Croupert's syndrome.

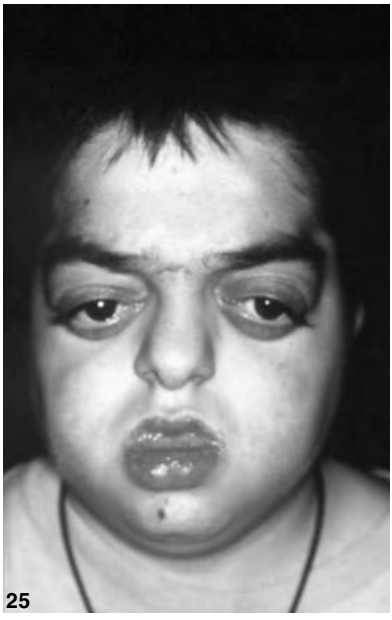
maxillary fossa, accounts for the marked reduction of the rhinopharyngeal respiratory space.

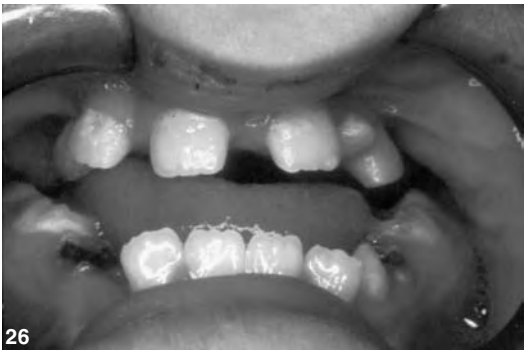
*Apert's syndrome*

The mode of transmission is of the dominant autosomal hereditary type. The cranial deformity frequently involves the coronal suture resulting in brachycephaly



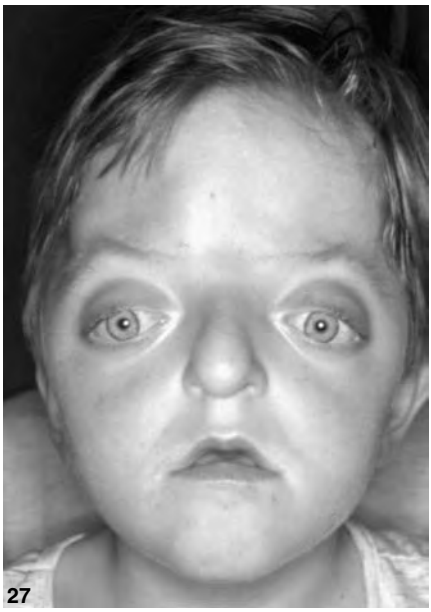



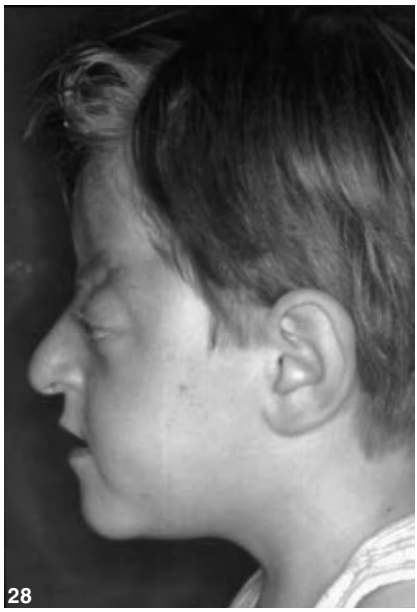



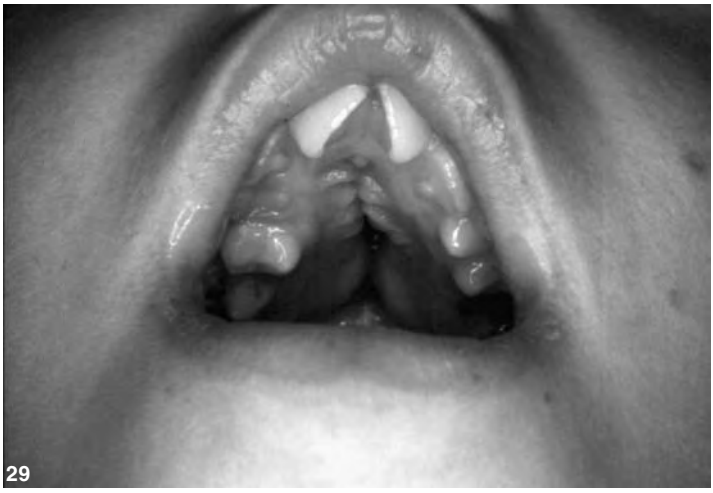

*Figs. 23-26.* Prospect and occlusal features of patients with Crouzon's syndrome.

and turricephaly (Figs. 27-29). Numerous cases of patients with mental retardation have been described in the literature.

The great wing of the sphenoid being involved in the deformity causes hypoplasia of the orbital-zygomatic-maxillary complex with anti-mongoloid in-




*Figs. 27-29.* Prospect, profile and detail of the palate of a patient with Apert's syndrome.

clination of the palpebral rim. Exophthalmos, when present, is far less severe than in Crouzon's syndrome.

In this syndrome, the upper jaw is also involved in the synostosis and in the ethmoid-sphenoid and fronto-temporal malformation. It is retruded, but the morphological changes involve the three planes of the space. A third class malocclusion is found with anterior overbite and open bite, as well as dental crowding.

Characteristic of Apert's syndrome is the presence of a cleft in the second-

ary palate, and syndactylia of both the hands and feet with fusion of the second, third and fourth fingers (Figs. 20 and 21), and only one large nail. Very occasionally, the thumb and little finger are involved in the syndactylia.

*Kleeblattschädel syndrome*

This syndrome, also known as triphyllocephalia, is a congenital syndrome characterized by a trilobate skull due to synostosis of the lambdoid and coronal sutures, associated with hydrocephalus and low implant of the ears. At a facial level, flattening of the nose is seen, together with hypertelorism and retrusion of the middle third, with consequent exophthalmos and anti-mongoloid inclination of the palpebral rim.

*Pfeiffer's syndrome*

This is a hereditary syndrome with dominant autosomal transmission. It is characterized by craniostenosis, and broad soles of the feet and big toes (Figs. 30 and 31). With regard to orbital, maxillary, and dental deformities, these are identical to those observed both in Crouzon's and Apert's syndromes.

*Achondroplasia*

This deformity is included in the group of craniofacial dysplasia with dyschondrosis. It is transmitted according to a dominant autosomal character and shows inadequate enchondral bone formation.

Therefore, it manifests with nanism and the typical short limbs, together with alterations in bone development at the craniofacial level. Due to the frequently associated massive development of the skull, disproportion with the facial structures is even more evident, and these appear to be retruded, despite regular bone development (Figs. 32-34).

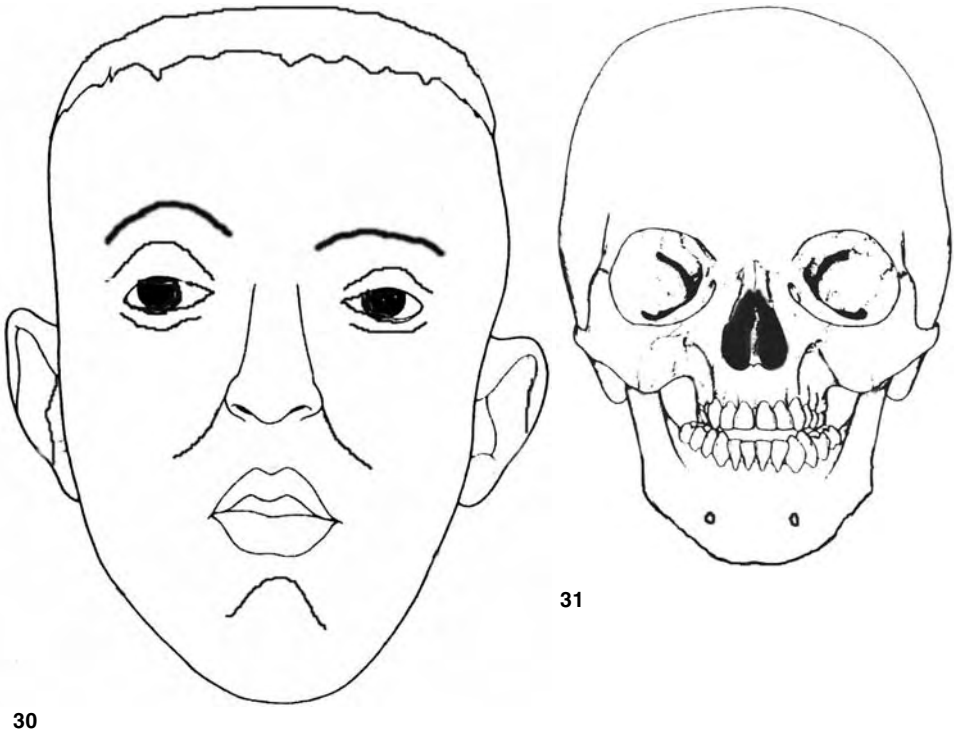
As is well known, of all the bones comprising the skull and face, only the cranial base is formed by the endochondral ossification process, and, therefore, its non-ossification causes the absence of growth of the orbital-nose-maxillary complex in a sagittal direction, which results in marked retrusion of the facial bone structure, with the exception of the mandible.

*Mandibular deformities*

This group includes both congenital and acquired deformities due to infections and degenerative or traumatic disease, occurring at a very early age, either at birth, or in the first years of life, but before complete development of the mandible.

In fact, as in orbital-zygomatic-maxillary complex malformations, the triggering element for the onset of OSAS is retrusion of the upper jaw, just as, in mandibular deformities, the triggering element is the reduced volume of the oral cavity caused by poor development of the mandibular branch and/or body, in some cases, associated with failure to open the mouth properly (Fig. 6).

Classification of congenital mandibular deformities is difficult, due to the



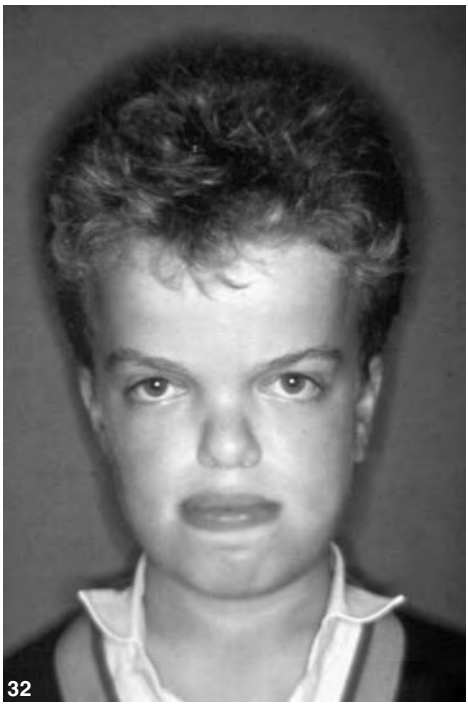
30 31

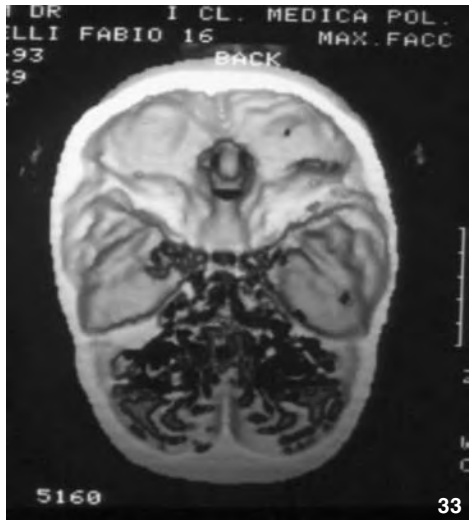
*Figs. 30 and 31.* Bony and soft tissue defects in patients with Pfeiffer's syndrome.

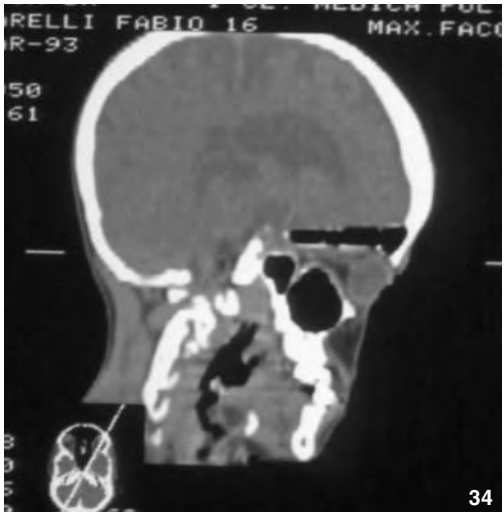
overlap of some symptoms. From a review of the literature, it can be seen that several authors have proposed various classifications, based, in some instances, on genetic evaluation, in others on clinical data, and others on classifications of all congenital craniofacial deformities (Gorlin *et al.*,[7] Franceschetti and Klein,[8] McNamara,[9] Stricker and Hepner,[10] Tessier,[11] Van der Meulen *et al.*[12]).

*Mandibular-facial dysostosis*, or zygoma-oto-mandibular dysplasia, Franceschetti's syndrome, and Treacher-Collins' syndrome (Figs. 35-39) are all terms used to define the same clinical pattern characterized by a bilateral deformity involving the temporo-zygomatic-auricular-mandibular area. Transmission occurs through a dominant gene with a variable expression. Many investigations have focused on the development of this malformation, and various pathogenic hypotheses have been advanced. It is generally held that the pathogenic moment coincides with a lesion during maturation, occurring at around the eighth week of fetal life (Fig. 40), due to a disorder in the neural crest from which many craniofacial structures are derived.

Describing the sites of the malformations from an analytical point of view, the orbit presents a larger axis orientated obliquely from the top to the bottom in a medio-lateral direction, while the infero-lateral region is in direct communication with the zygomatic-maxillary complex. Naturally, this gives rise to



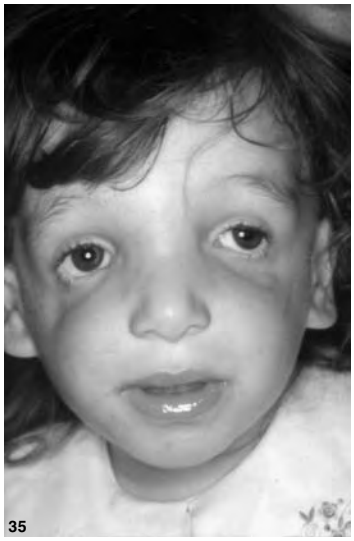

*Figs. 32-34.* Patient with achondroplasia: 3D-CT and CT sagittal images.

enophthalmos due to prolapse of the orbital contents in the zygomatic-maxillary complex, and an anti-mongoloid orientation of the palpebral rim. Hypoplasia and interrupted ossification of the zygoma explain the flattening of this region, and the presence of the lateral coloboma of the lower eyelid. The upper jaw does not present with hypoplasia; on the contrary, due to the lack of oc-

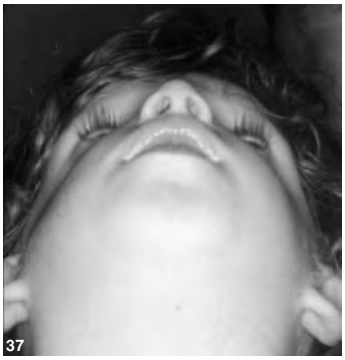
clusal control on behalf of the mandible, this may be underdeveloped both in a sagittal and a vertical direction. Choanal atresia may even occur.

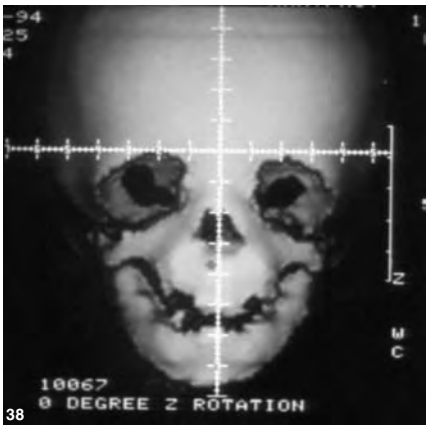
Morphological changes may be detected in the external and middle ear, however, these are not as severe as those in the facial microsomia.

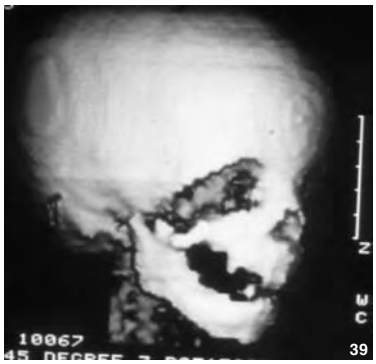
The most severe respiratory disorders are caused by mandibular deformities; in fact, the mandible is small, the ramus often being involved, with condyle deformities of variable entity, which, however, do not induce ankylosis of the temporo-mandibular joint; the antigonial incisure is particularly accentuated, and the chin is set far back giving the impression of a typical bird-beak profile. The choanal atresia and the disproportion between the reduced volume of the oral cavity with respect to that of the tongue, explain the pathogenic mechanism of the respiratory disorder. In some cases, the respiratory disorders may be extremely serious and even have a dramatic outcome; once these respiratory








*Figs. 35-39.* Patient with Treacher-Collins' syndrome: frontal, lateral, and axial views, and 3D-CT images.

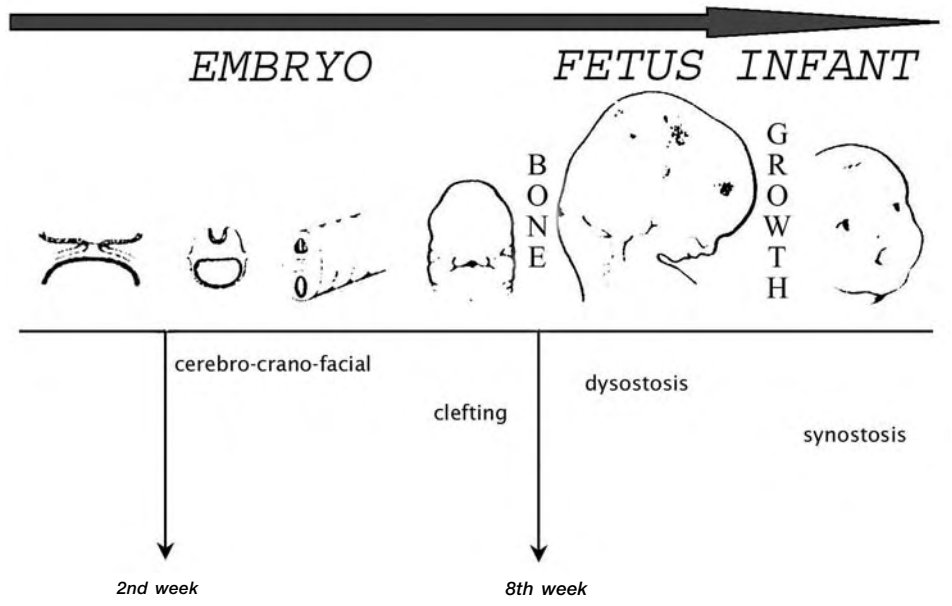
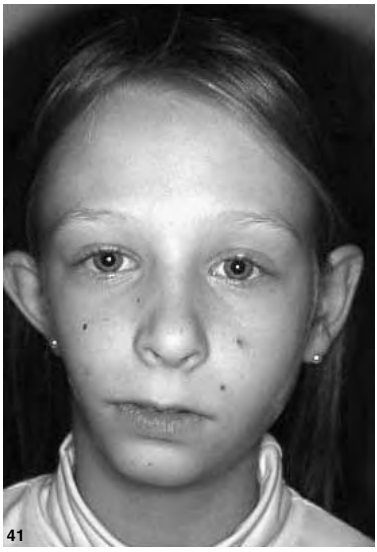


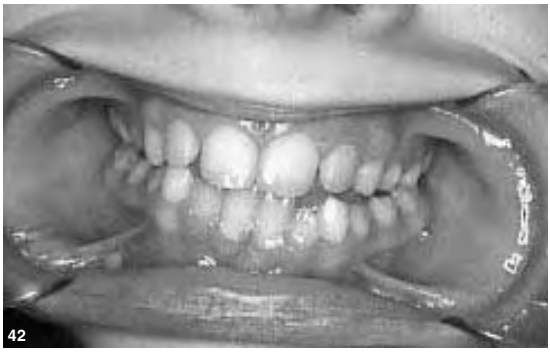

*Fig. 40.* Diagram of embryonal and fetal development.

crises have been corrected, the growth of the young patients protects them from life-threatening episodes, and it is possible to start treatment, both for the functional disorders and the esthetic aspects.

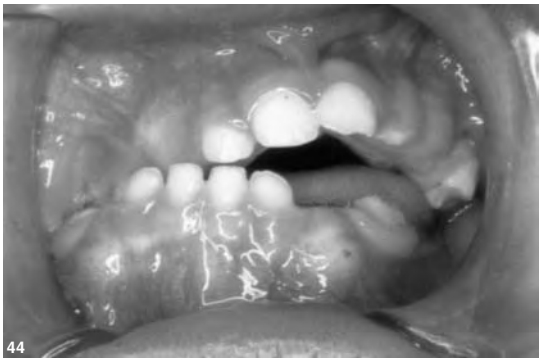
*Facial microsomia*, or oto-mandibular dysplasia (Figs. 41-44), are terms used to define undersized skeletal, nervous, vascular and muscular structures, derived from the first and second branchial arch. The malformation is usually monolateral, even if it may, occasionally, present bilaterally, and involves the temporal, zygoma, maxillary, and mandibular structures, as well as the temporo-mandibular joint; moreover, the temporal, masseter, and pterygoid muscles, as well as the outer and middle ear may be involved. The severity of the case will, of course, vary considerably, depending upon the structures involved and the extent of their involvement, and may range from slight to very evident forms. Therefore, it is possible to observe cases in which only the auricle presents with slight defects, while other cases present with total subversion, or even total absence of the auricle. Likewise, when skeletal (Figs. 45-48) and muscular tissues are involved, it is possible to observe cases in which the mandibular deformity is only very slight and also the muscular hypoplasia is very slightly accentuated, or, again, cases with morphological subversion of the different components of the ramus (from the temporo-mandibular joint to the whole ramus), or even of the mandibular body; in the extreme forms, very severe hypoplasia of the zygoma may be observed, also associated with flattening of the temporal fossa, orbital dystopia, facial cleft, and hypertelorism. Macrosto-

mia with cleft of the labial angle may also be seen. The more severe the morphological changes of the bone structures, the more severe the muscular and nervous hypoplasias. On the other hand, the morphological changes at the level of the auricle are not related to the severity of the bone and soft tissue lesions (Fig. 49). Many authors[13-19] have made several attempts, from their own points of view, to classify the different forms of this deformity. Pruzansky[14] proposed a classification based on the alterations of the mandible. Chierici,[20] on the other hand, focused his attention on the alterations to the temporo-mandibular joint, while Lauritzen and co-workers[15] suggested a classification based on the

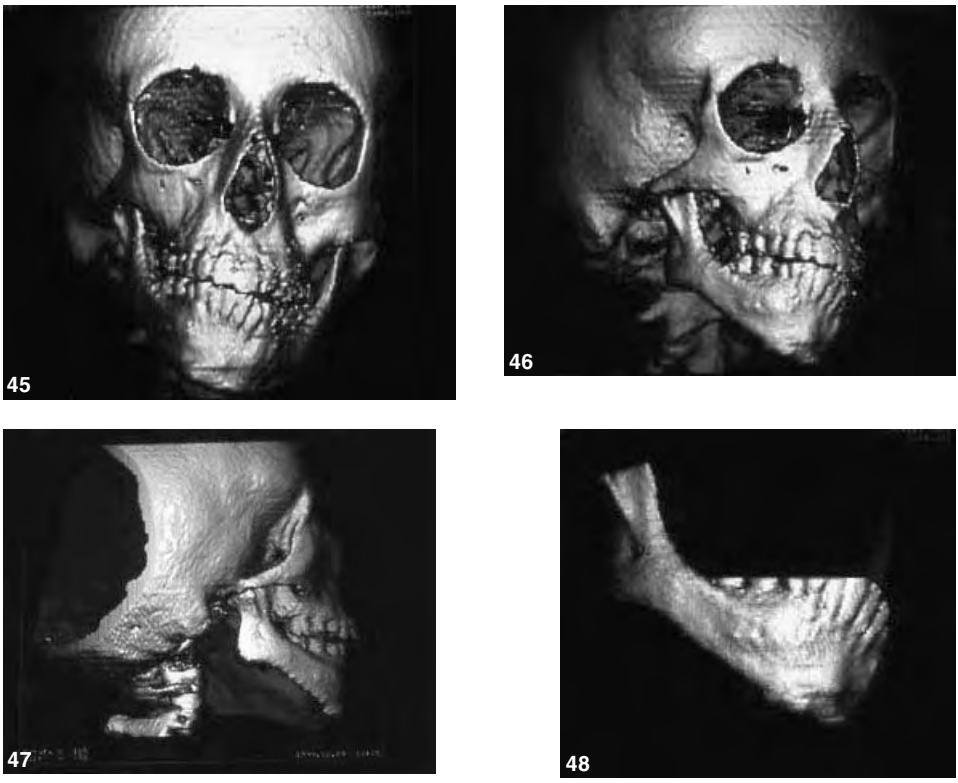







*Figs. 41-44.* Patients with hemifacial microsome: frontal views and occlusal images.




*Figs. 45-48.* 3D-CT images of a patient with hemifacial microsome.

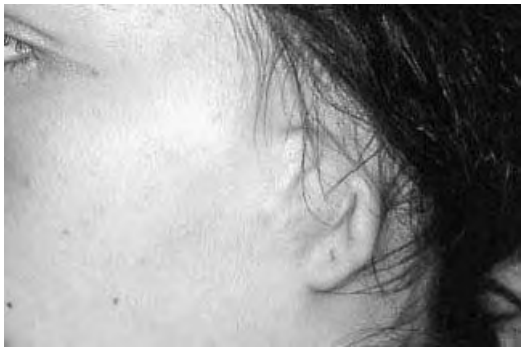


*Fig. 49.* Detail of the auricular outline in a patient with hemifacial microsome.

mandibular-zygomatic defects. David *et al.*[17] took into consideration lesions involving the bony, auricular, and soft tissues (SAT; Table 1), while Vento *et al.*[18] suggested a classification bearing in mind alterations involving the orbit, mandible, ear, nerves, and soft tissues (OMENS; Table 2).

Unlike other deformities, for which explanations have been offered, etiopathogenesis of the facial microsomia still remains to be elucidated. Rarely

*Table 1* SAT classification

| | |
|---|---|
| *Bony tissues* | |
| S1 | small mandible with normal form |
| S2 | condyle, branch, and sigmoid incisure identifiable, but roughly altered; mandible remarkably different from the standard regarding form and dimension |
| S3 | mandible seriously deformed, from difficult identification of the components of the branch to complete agenesis |
| S4 | mandible altered as in S3, associated with orbital deformity due to serious hypodevelopment of the zygoma, and anti-mongoloid orientation of the palpebral fissure |
| S5 | same alteration as S4, associated with orbital dystopia, and frequently with hypoplasia and cerebral asymmetry with flattening of the temporal fossa |
| *Ear* | |
| A0 | normal |
| A1 | small deformed auricle, which however maintains normal characteristics |
| A2 | rudimentary hook-shaped auricle in the cranial part corresponding to the helix |
| A3 | same alterations as A2, also associated with a deformity of the lobule and absence of support of the pinna |
| *Soft tissues* | |
| T1 | minimum deficit of contour without involvement of the cranial nerves |
| T2 | moderate defects |
| T3 | more evident defects with facio-scoliosis, possible serious hypoplasia of the cranial nerves, parotid gland, and masticatory muscles; ocular involvement; facial or labial schisms |

*Table 2* OMENS classification

| | |
|---|---|
| *Orbit* | |
| O0 | normal orbit for dimensions and position |
| O1 | alteration of orbit dimensions |
| O2 | alteration of orbit position |
| O3 | alteration of orbit position and dimensions |
| *Mandible* | |
| M0 | normal mandible |
| M1 | mandible and glenoid cavity have reduced dimensions with a short branch |
| M2 | mandibular branch is short and with an altered form. A further subdivision of A and B is carried out, according to the position of the condyle and of the temporo-mandibular articulation |
| M3 | absence of the branch of the glenoid cavity, and of the temporo-mandibular articulation |
| *Ear* | |
| E0 | normal ear |
| E1 | minor hypoplasia |
| E2 | absence of the external auditory canal, variable hypoplasia of the concha |
| E3 | bad positioning of the lobule and auricular agenesis |
| *Facial nerve* | |
| N0 | no involvement of the facial nerve |
| N1 | involvement of the upper bundles of the facial nerve (temporal and zygomatic branches) |
| N2 | involvement of the lower bundles of the facial nerve (buccal, mandibular, and cervical branches) |
| N3 | involvement of all the bundles of the facial nerve |
| *Soft tissues* | |
| S0 | no evident involvement of the soft tissues |
| S1 | minimum involvement of the subcutaneous muscles |
| S2 | moderate involvement of the soft tissues (between S1 and S3) |
| S3 | serious involvement of the soft tissues |

have cases of familiarity of this deformity been reported. That the damage occurs between the first and eighth months of fetal life now appears to be generally accepted, and it is likely that the noxa patogena acts on embryonal development during this period. Various causes have been taken into consideration (drugs, toxic substances, etc.), but they all involve vascular lesions (hemorrhage, hematoma, spasm) of the stapedial artery, or the territory which it supplies. In experimental studies on the rat and hamster, Poswillo[21] reproduced an embryonal hematoma due to thalidomide (a drug that causes hemorrhage), which induced lesions identical to those observed in facial microsomia.

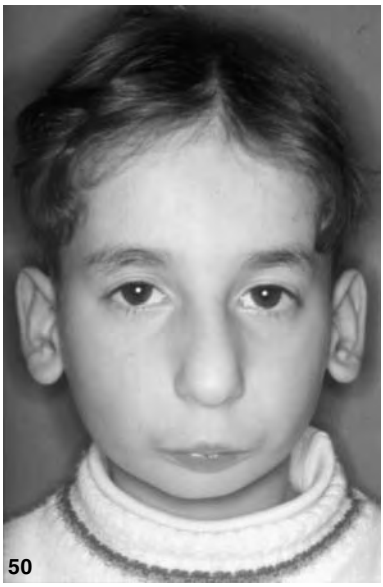
On the other hand, more recently, Cousley and Wilson[22] advanced the hypothesis of a multifactorial etiology responsible for the impaired development of Meckel's cartilage (dyschondrogenetic theory).

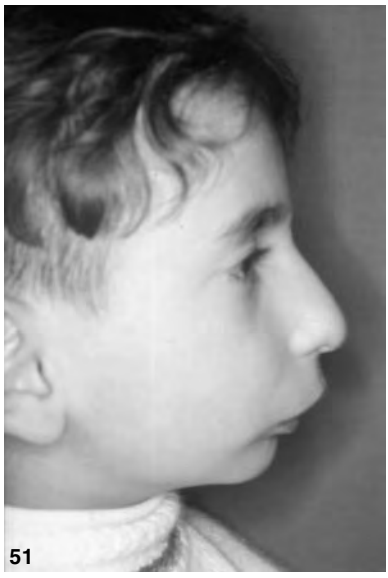
*Pierre Robin syndrome* (Figs. 50-56).
This syndrome presents with very distinctive characteristics, not only on account of the severity of the deformities themselves, but also due to the level of the apneic crises (which vary in both number and severity). Indeed, the younger the patient, the more dramatic the evolution. The syndrome is also known as Pierre Robin sequela due to the relationship of the etiopathogenetic aspects of the clinical signs responsible for the particular pattern of the malformation: mandibular micrognatia; glossoptosis; and cleft palate.

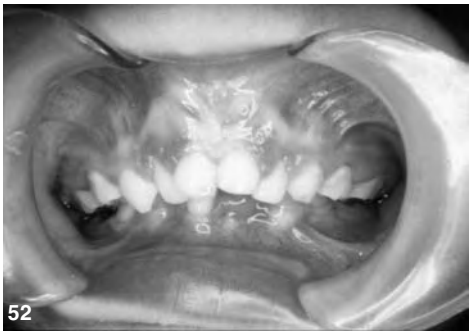
The deformities are present at the upper jaw and mandibular level. In fact, microretrogenia is often associated with cleft palate.

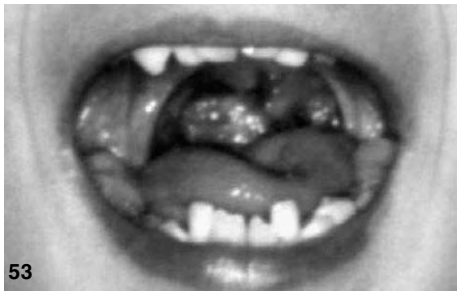
The pathogenesis depends on mechanical causes during fetal life, even if neuromuscular lesions are present at the level of the masticatory muscles, tongue, and pharyngeal-palatal muscles. In practice, extension of the head cannot be completed, due to the lack of anticlockwise rotation of the mandible; the tongue stays wedged in the midline of the palate preventing fusion, and thus causing cleft palate. Again, due to mechanical compression on the temporo-mandibular joint, a varying degree of ankylosis almost always occurs. At birth, a micromandible, associated with glossoptosis and immaturity of the involved muscles, is responsible for severe respiratory crises. Intubation or tracheotomy of very young patients may be necessary while waiting for the mandible to develop, which may be either spontaneous or surgically-assisted. Surgical closure of the cleft palate will obviously be necessary in order to reconstruct the anatomical integrity of the palate, and to prevent the tongue from becoming wedged and further reducing the respiratory space.

Postnatal postural and functional treatment is also extremely important. In fact, an obstructer plaque is applied in order to artificially reconstruct the roof of the palate, and dummies and feeding bottles are used to stimulate lowering and propulsion of the tongue, reduce glossoptosis and the severity and frequency of apneic crises, and, furthermore, to stimulate mandibular growth.



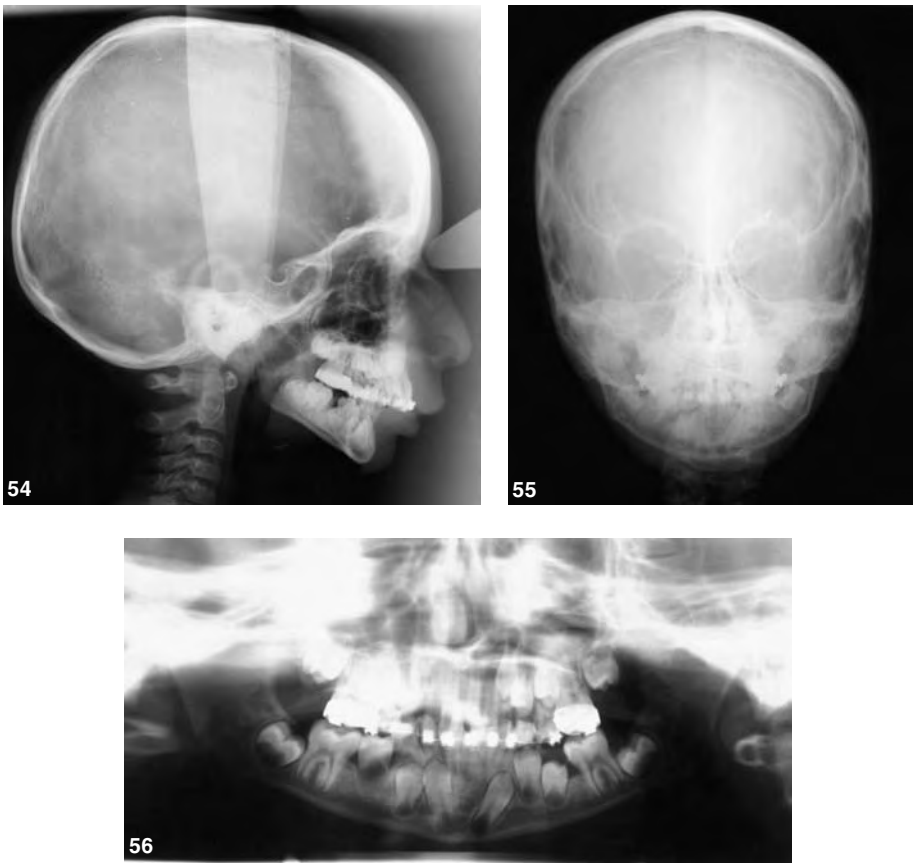




*Figs. 50-53.* Patient with Pierre Robin syndrome: frontal, lateral, occlusal views, and details of the palate.

*Microgenia due to ankylosis* (Figs. 57-77)

It is well known that trauma of the temporo-mandibular joint can, in some cases, lead to a more or less important structural subversion of the articular components. However, the consequences triggered by trauma of the same kind in subjects during developmental age differ considerably in comparison to those in adults. In fact, in a growing subject, more or less complete interruption of mandibular growth may be associated with strictly articular damage, which, as is well known, occurs due to apposition of the bone at the level of the condyle, the true center of mandibular growth. The causes that induce ankylosis occur even during prenatal life, on account of the incorrect position during pregnancy, but more simply on account of a dystocia delivery due to ischemic necrosis resulting from compression of the condylar head.

After birth, even an accidental fall, often disregarded, during the first few years of life, but before the end of bone growth, which coincides with the

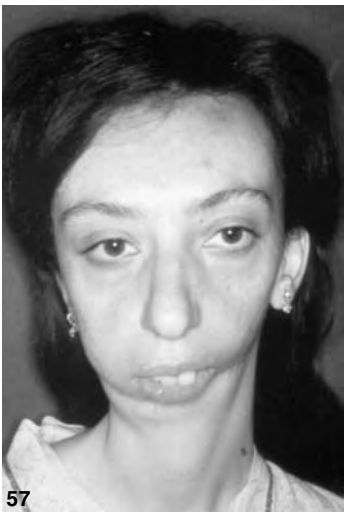


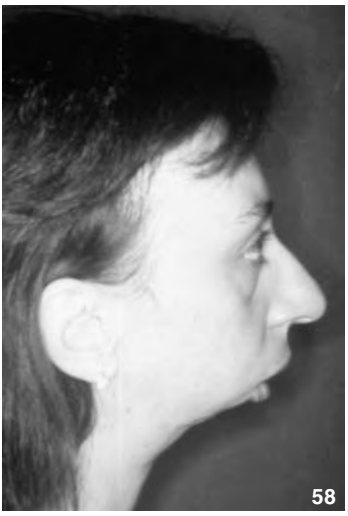

*Figs. 54-56.* X-ray of a patient with Pierre Robin syndrome.

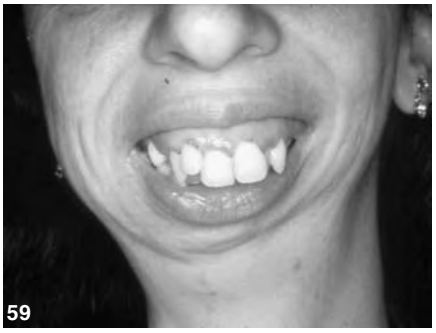
completion of permanent dentition, may result in temporo-mandibular ankylosis, due to a lack of adequate functional and/or surgical treatment. Finally, it should not be forgotten that lesions at joint level may also be triggered by infection or toxic factors.

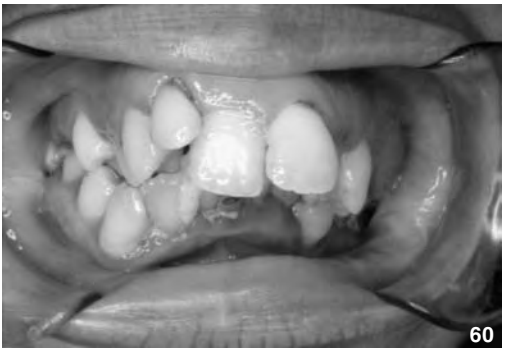
Regardless of the cause of the ankylosis, the consequences are structural damage of the articular components and of the mandible, especially the ramus. Alterations in the temporo-mandibular joint may vary from cases in which identification of its components is still possible, to cases in which the ramus is completely fused with the temporal bone, and normal anatomical elements are no longer detectable. The mandibular ramus appears to be reduced in a vertical direction, and the more closed the ankylosis, the more the antigonial incisure is revealed.

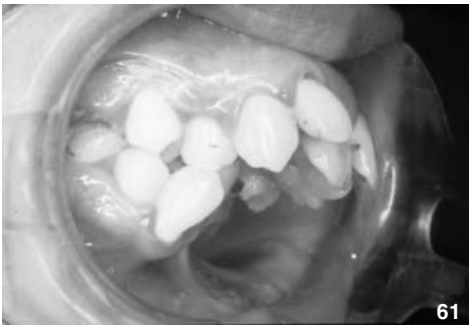
Therefore, the gonial angle appears to be more open, while in monolateral ankylosis, the mandibular body is short with deviation of the chin on the side of the lesion, and compensatory hyperdevelopment on the opposite side. On the other hand, in bilateral forms, the body, even if extremely reduced in length,



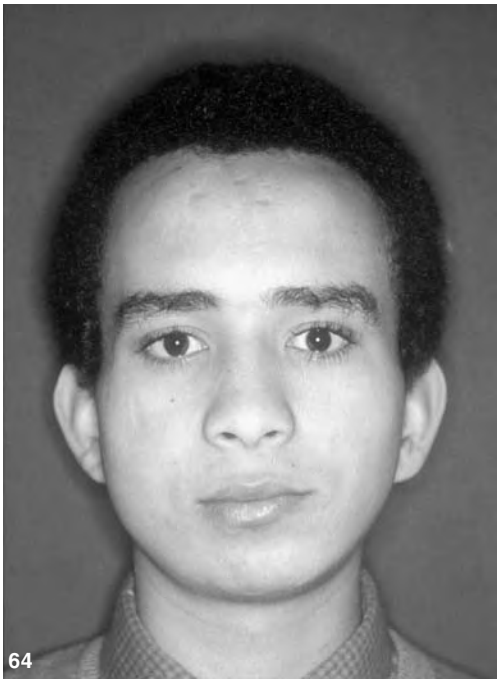



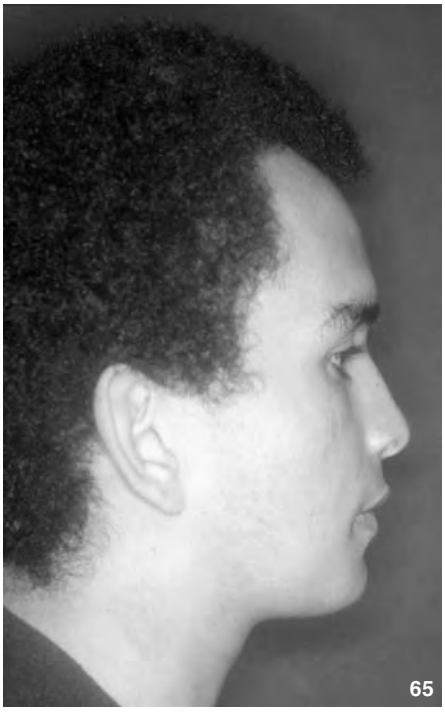



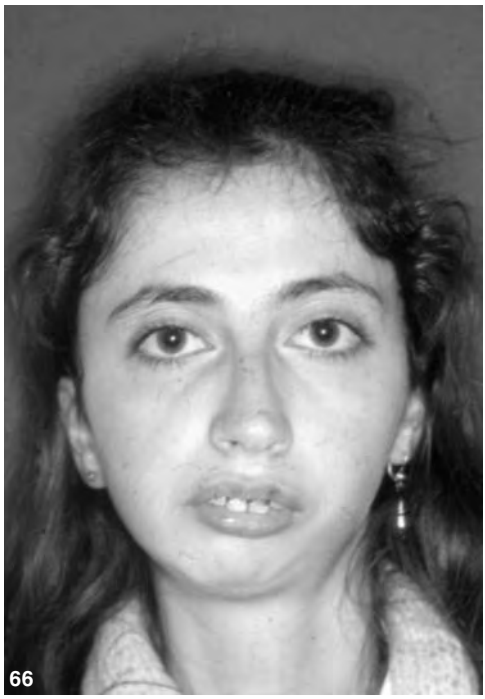

*Figs. 57-61.* Patient with secondary microgenia with post-traumatic ankylosis: frontal, lateral views, and occlusal details.

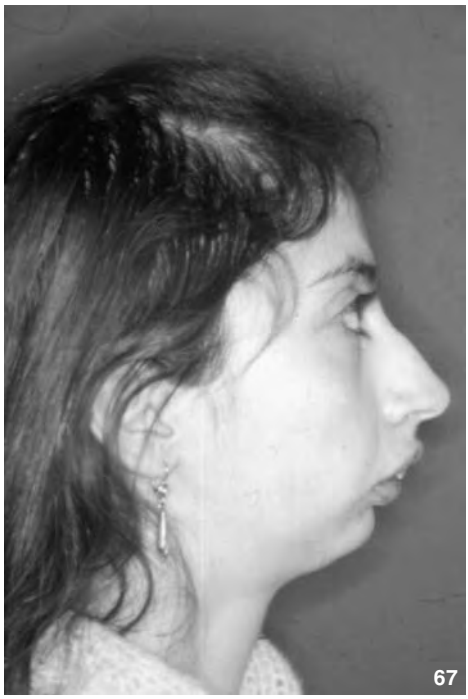


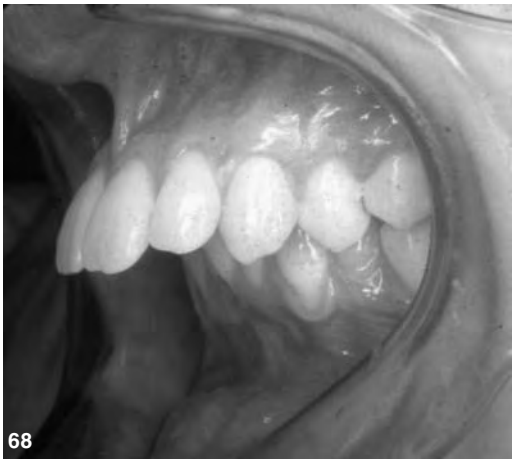


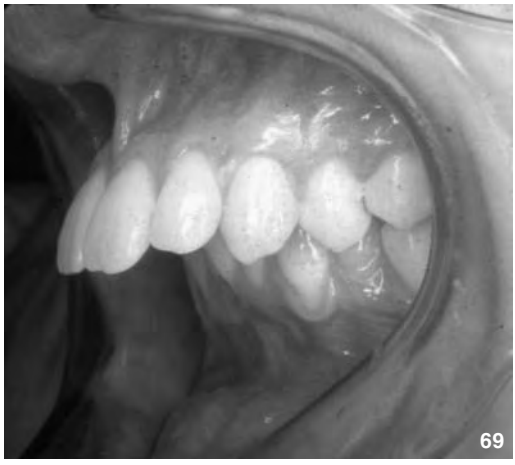




*Figs. 62-65.* Patient with monolateral temporomandibular joint (TMJ) ankylosis: pre- and post-operative results.



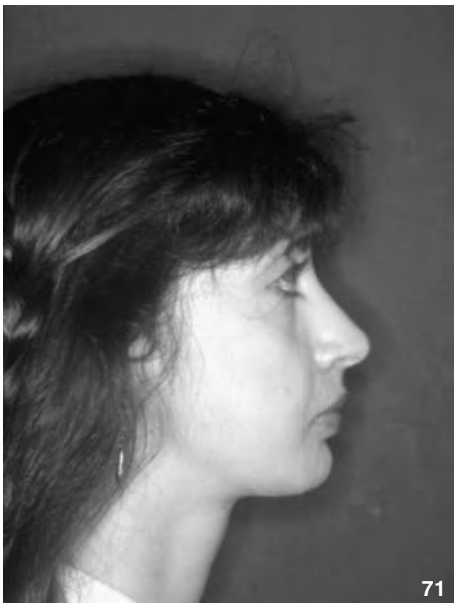



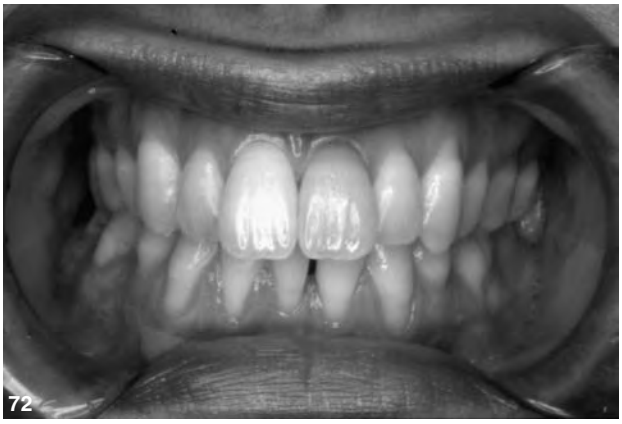




*Figs. 66-69.* Patient with secondary microgenia and post-traumatic ankylosis: frontal and lateral views, and occlusal details.

maintains its symmetry, whereas the chin rotates clockwise, thus creating the characteristic bird-beak profile.

In the very evident forms, the dimension of the oral cavity is completely inadequate as far as the volume of the tongue is concerned, which obstructs the passage of air in the inspiratory phase (Fig. 74) and, in these cases, tracheostomy may be mandatory.

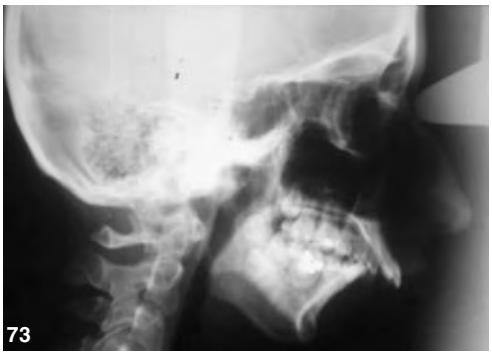



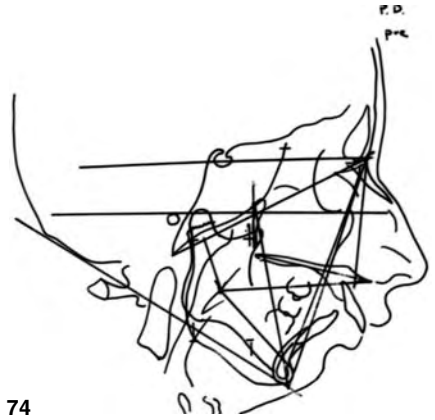

*Figs. 70-72.* Postoperative results.

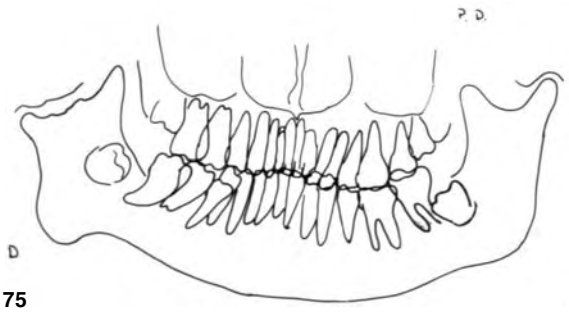
## Surgical techniques

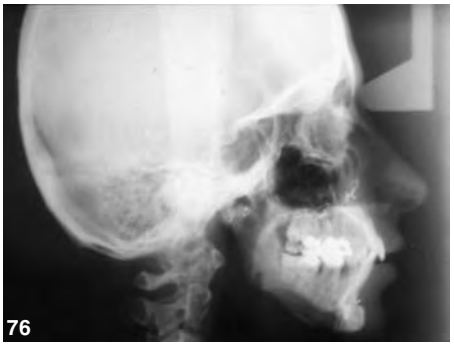
Surgical treatment of craniofacial deformities responsible for OSAS has undergone a remarkable evolution, passing from tracheotomy, which can be defined as a purely symptomatic treatment, to a variety of surgical procedures aimed at eliminating the cause of the obstruction in the upper airway.

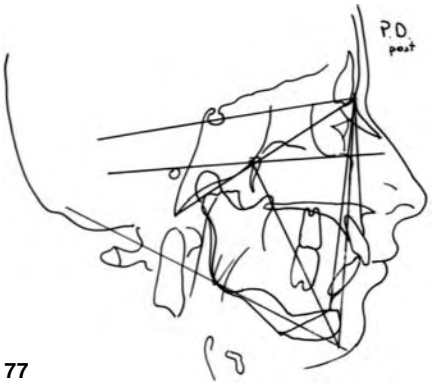
It is worthwhile recalling here that it is mandatory to formulate a correct diagnosis of the cause of OSAS. In fact, whilst in some deformities diagnosis is relatively easy, in other adult forms, the impairment responsible for the pathological pattern must be very carefully evaluated, inasmuch as there are several




*Figs. 73-77.* X-ray, and pre- and postoperative cephalometry.

surgical procedures, which may, on the contrary, vary radically depending upon the triggering factor.

For a long time, tracheotomy was considered the treatment of choice in the management of upper airway obstruction, but, nowadays, this technique is used as a support in the actual surgical treatment. However, the tendency is to eliminate it as soon as possible in order to avoid the well-known problems related to

tracheotomy in infancy, with possible malacia of the trachea and difficulties in decannulating the patient.

Obstructions in the rhinopharyngeal space are usually successfully treated by removal of the obstacle causing them. Therefore, it is possible to pass from adenoidectomy and/or tonsillectomy to uvulopalatopharyngoplasty (UPPP), which was introduced by Ikematsu, in 1964, and used in the correction of the OSAS by Fujita *et al.* in 1981.[23] Other surgical procedures have been proposed with the use of the $CO_2$ laser, also for the correction of nasopharyngeal stenosis following UPPP.

Intrapalatine resection (IPR) has also been used, which consists of resection of the entire thickness of the proximal portion of the soft palate, the shape of which can be compared to a slice of orange.[24] The extent of the excision, which depends upon the dimensions of the soft palate, varies between 15 and 30 mm, and is carried out between the hard palate and the free edge of the soft palate.

Depending upon their particular needs, operations are carried out to remove choanal atresia, or other rhinopharyngeal obstructive pathologies. Other operations, such as partial glossectomy or hyoidopexy (Fig. 78), whether or not associated with myotomy of the geniohyoid and stilohyoid muscles, may be taken into consideration provided structural and positional maxillary deformities do not coexist.

On the other hand, some cranio-maxillo-facial deformities require a specific surgical procedure, not only aimed at eliminating encephaloceles, but also at three-dimensional repositioning of the maxillary and/or mandibular bony structures involved in the deformity. An extraordinary evolution has taken place in the surgical treatment of these cases, usually allowing successful morphological and functional results to be achieved.

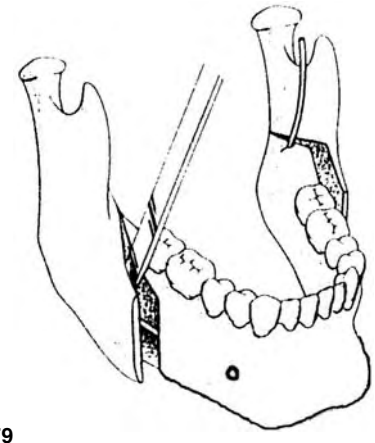
We have witnessed a gradual change from surgical procedures aimed at partial mandibular osteotomies (Figs. 79 and 80) to combined operations of maxillo-mandibular osteotomy, and then to 'monobloc' advancement of the facial complex, and finally, to complex craniofacial osteotomies (Figs. 81-84). Recently, bone distraction has become current practice, allowing progressive advancement of a considerable amount of facial bone (Figs. 85-89); this technique is particularly suitable for pediatric patients.

*Surgical treatment of cephaloceles*

The aim of this treatment, apart from the neurosurgical implications, is the removal of herniated masses in the rhinopharyngeal space, and reconstruction of the bony breach of the cranial base. During the same operation, it is often worthwhile proceeding with correction of the orbital dystopia, or of the orbital hypertelorism resulting from the primary pathological factor.

For successful results, frontal, fronto-orbital, fronto-nasal flaps (Figs. 90-98) are prepared by means of a bicoronal incision associated with subpalpebral and/or intraoral incisions. The first step consists of identification of the cepha-

*Fig. 78.* Diagram of hyoidopexy.



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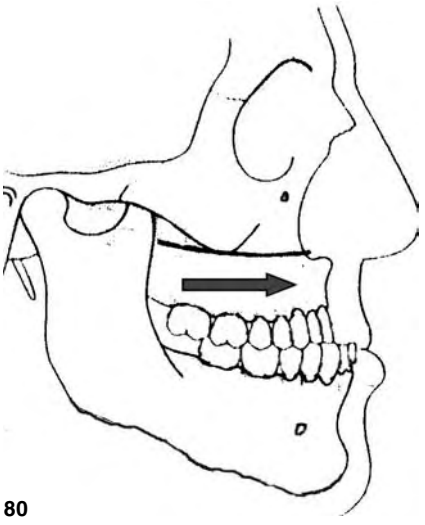

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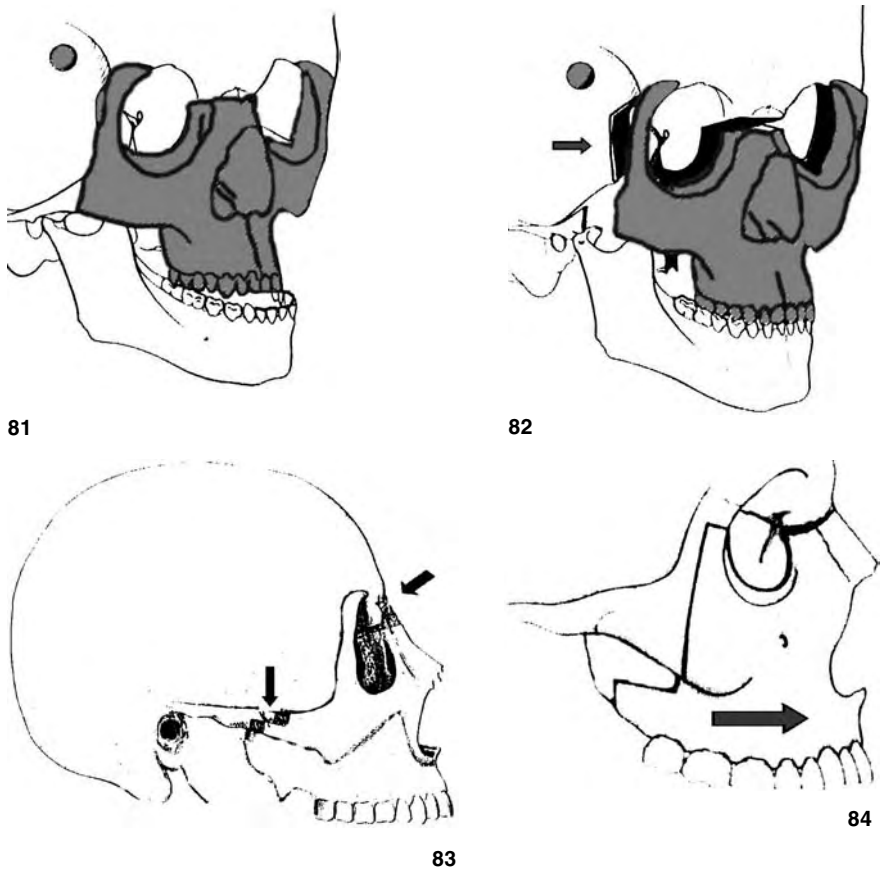
*Figs. 79 and 80.* Diagrams of sagittal osteotomy of the mandible, and Le Fort I maxillary osteotomy.

locele, which is excised, and in reconstruction of the possible dural breach. Ostetomy is then carried out to correct the ethmoid-orbital space. The extent of correction of the bony structures is established prior to surgery, according to three-dimensional evaluations obtained with 3D-CT. The esthetic and functional results depend upon the precise analysis of the images, and upon the



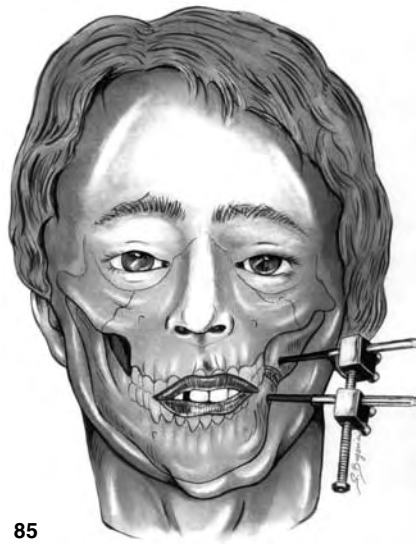

*Figs. 81-84.* Diagrams of complex facial osteotomies.

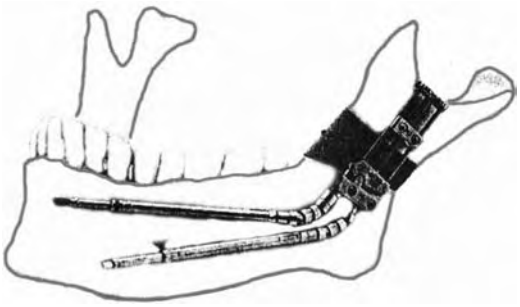
accuracy of reproducing them in the operating theater. Stabilization of the repositioned bony structures is carried out with titanium microplaques in adults, and with reabsorbable plaques in patients who are still growing.

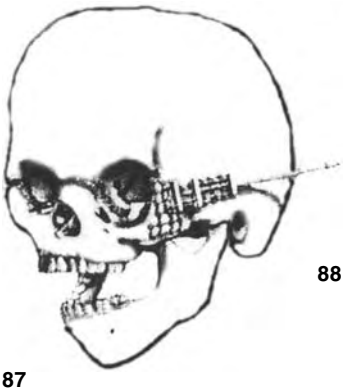
*Surgical treatment of craniofacial deformities triggering obstructive sleep apnea syndrome (upper third and middle third)*

Cranio-maxillo-facial deformities can lead to OSAS when the nasopharyngeal respiratory space is found to be reduced on account of displaced bony structures. Before the techniques for mobilization of the cranial and facial bones had been developed,[25-27] symptomatic therapy was the only treatment available.

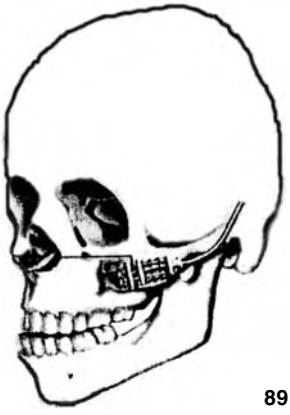
The surgical steps of craniofacial osteotomies consist of subperiosteal exposure of the bones involved, through esthetically acceptable accesses or areas not immediately visible, and in their mobilization, whilst maintaining the vascular-nervous structures connected to them integrally. The choice of the various osteotomies and their possible association depends on the type as well as on the severity of the deformity to be corrected. The most used osteotomies in



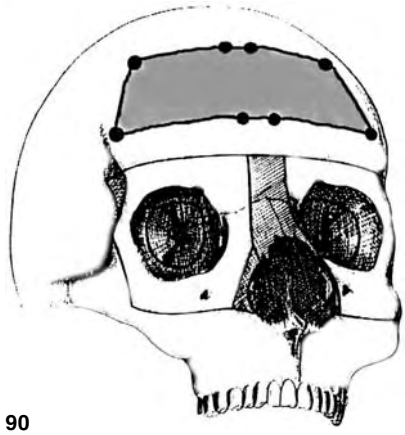





*Figs. 85-89.* Diagrams of various mandibular and maxillary distractor devices.

this field are those for correction of orbital dystopia and for advancement of the entire facial complex, or just the upper jaw.

During orbital correction, osteotomy of all the walls may be necessary, in which case, a combined neurosurgical and maxillofacial approach is mandatory (Fig. 90). If, on the other hand, osteotomy of the orbital roof is not required, then the infrabasal approach will be sufficient (extra-cranial). In the former case, a bicoronal incision is made prior to exposure of the frontal region, nasal bones, medial wall with the lacrimal groove, and lateral wall of the orbit, releasing the temporal muscle from the homonymous crest. The lower wall is exposed through an incision in the lower eyelid or, for esthetic reasons, through the conjunctiva. Then, safeguarding the supraorbital nerve, a frontal flap is fashioned. Once the latter has been removed, it is possible to proceed with detachment of the dura of the anterior cranial fossa up to the clinoid.



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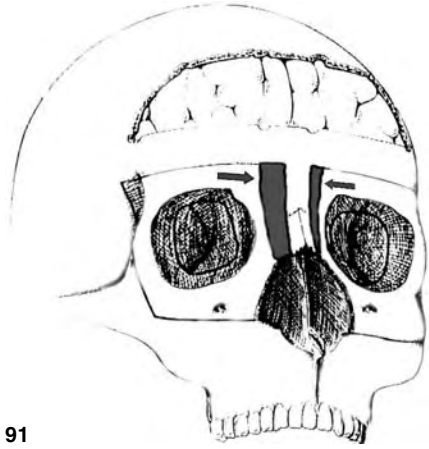

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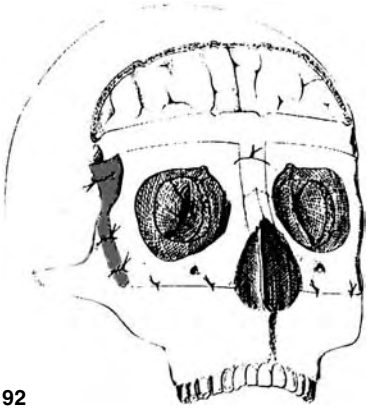

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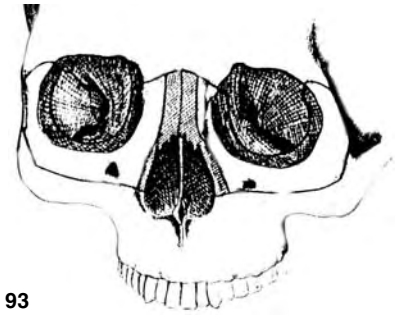

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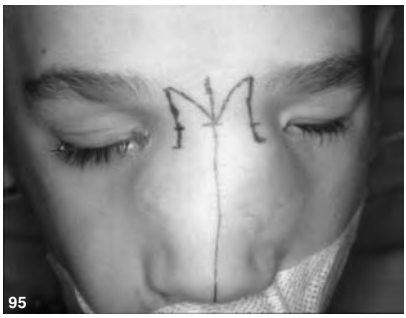
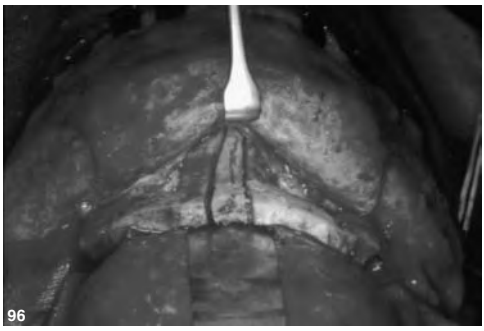
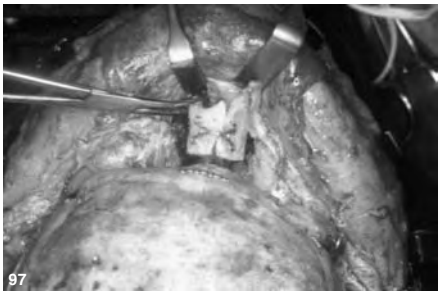
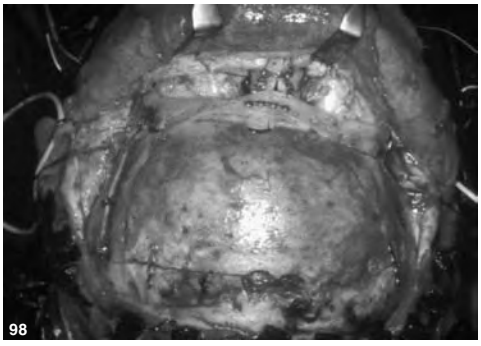
*Figs. 90-94.* Diagrams of fronto-orbital-nasal osteotomies.




*Figs. 95-98.* Intrasurgical images. Preparation of fronto-orbital-nasal flaps and repositioning after correction of hypertelorism.

At this point, it is possible to carry out orbital osteotomies. These, inside the orbit, form a line that passes along the roof, the papiracea lamina posteriorly to the tear duct, the apex of the lower orbital fissure, the spheno-zygomatic suture, and the great wing of the sphenoid. Externally, the osteotomy line has to be extended from the infero-medial edge of the craniotomy to the frontal process of the upper jaw, continuing at a right angle along the lower orbital edge, below the second branch of the fifth cranial nerve, to include the entire body of the zygoma. After all the osteotomies associated with interruption of the zygomatic arch have been performed, mobilization of the orbital frame is possible. It should be borne in mind that the closer the osteotomy passes the apex, the more the orbital volume will be increased. While orbital mobilization is being carried out, it is possible, at the same time, to perform uni- or bilateral, symmetric or asymmetric, ethmoid resection for correction of the hypertelorism which may possibly be associated.

If osteotomy of the orbital roof is not planned, the same incisions will be made, with the exception of the neurosurgical step. Therefore, after exposure of the orbital walls, the osteotomies start laterally at the level of the fronto-zygomatic suture, and medially at the level of the fronto-nasal suture, to be reconnected exactly as in the former case. Therefore, as planned, it will be possible to move the three orbital walls, with the exclusion of the upper one.

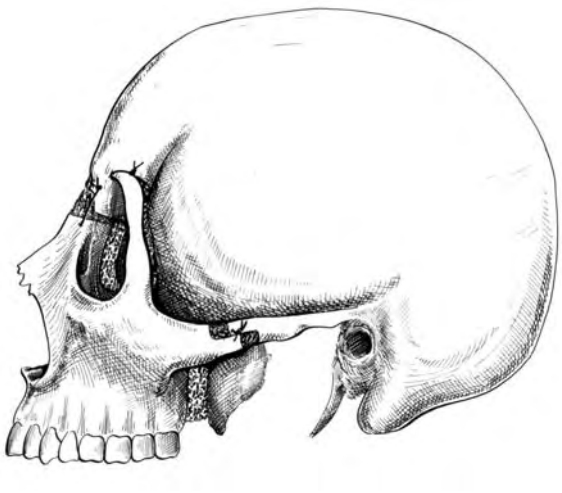


*Fig. 99.* Osteotomies for the mobilization of the facial middle third.

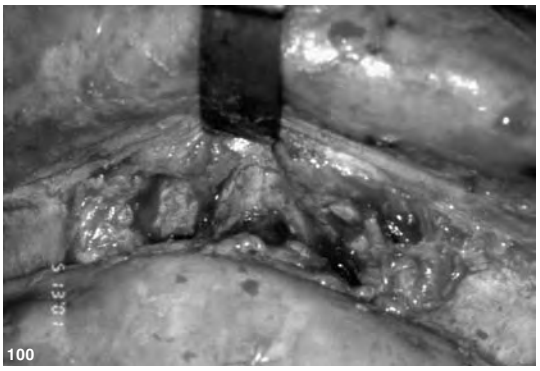
In total mobilization of the facial complex (Figs. 81-83), a bicoronal incision and an incision of the gingival fornix are made, corresponding to the pterygoid incisure.

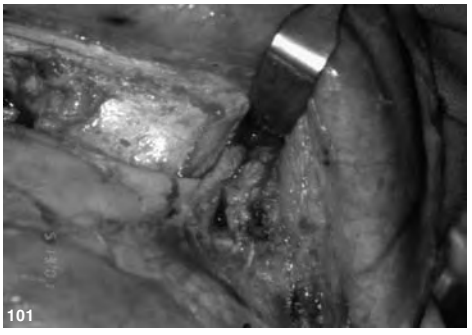
Through the former, the fronto-nasal and fronto-zygomatic sutures are exposed, from where the osteotomies will commence. While the endo-orbital osteotomy lines follow those of the orbital mobilization via the infrabasal approach, for the extra-orbital osteotomies, only interruption of the zygomatic arch can be anticipated (Fig. 99) and, through an intraoral approach, interruption of the pterygo-maxillary junction suture is performed. In this phase, by applying Rowe forceps via the naso-palatal approach, it is possible to make strong traction movements on the facial complex, both downwards and sideways, until complete detachment from the connections with the cranial bones is achieved.

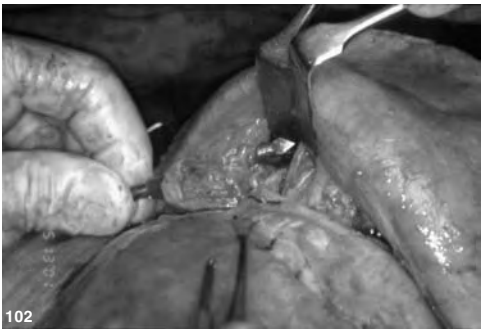
At this point of the procedure, it is possible to apply rigid fixation systems, with reabsorbable or non-reabsorbable mini-microplates, in order to maintain the movements of the facial complex in a sagittal and vertical direction. Alternatively, and particularly in the case of very young patients, bone distraction systems may be used, which, within a few weeks, allow more important movements to be achieved compared to those that can be obtained during the surgical phase alone (Figs. 100-108).

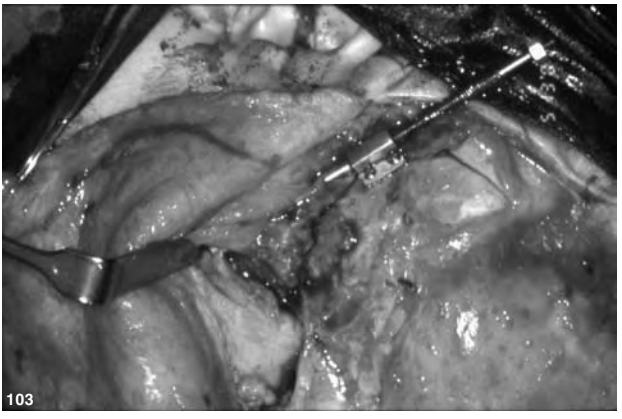
*Mobilization of the upper jaw*

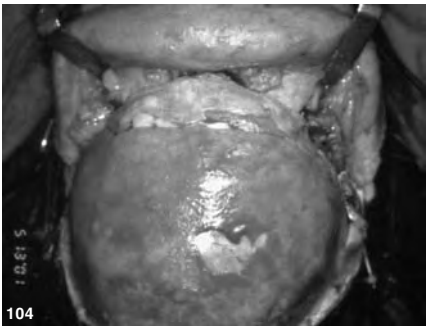
LeFort I is an extremely popular operation in orthognatic surgery (Figs. 80, 109-111). It is based on experience in traumatological cases and on studies of vascularization of the maxilla. It is indicated in adult patients with a third class occlusion, and orthodontic preparation is necessary in order to obtain normal occlusion at the end of the operation. This consists of detachment of the upper



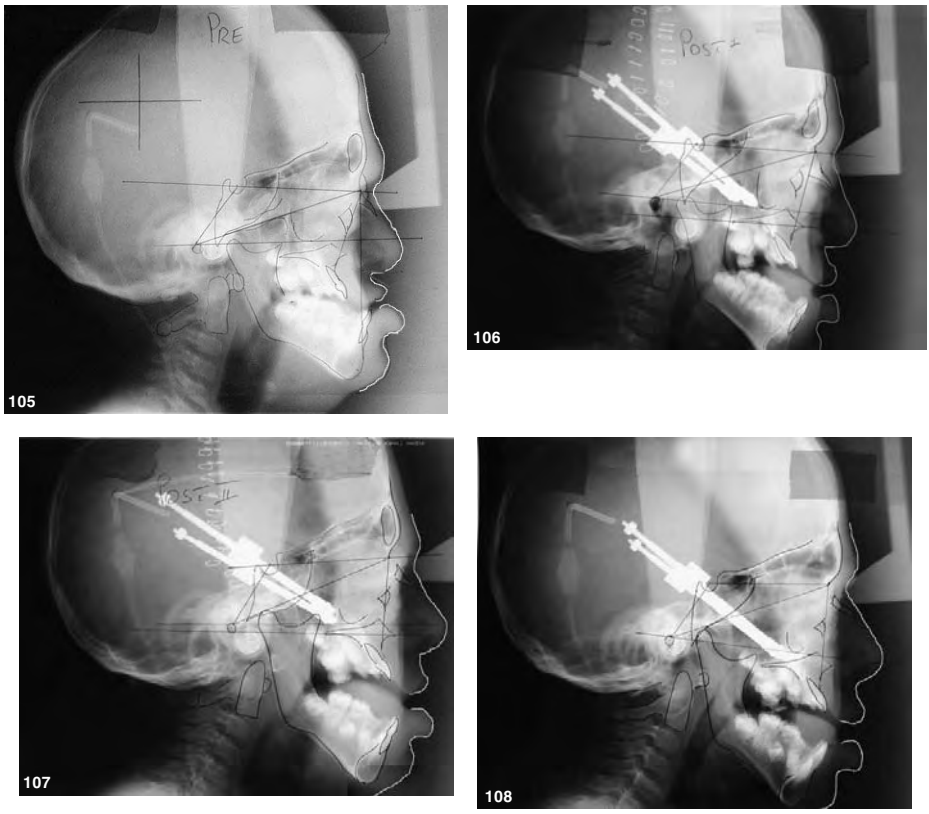



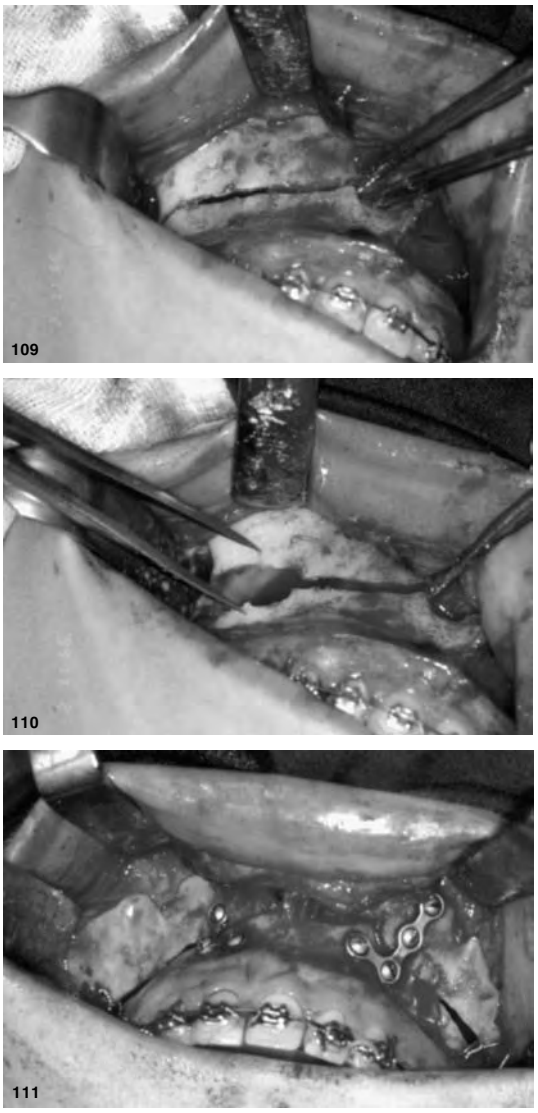




*Figs. 100-104.* Intraoperative images: preparation of advancement osteotomies of the facial complex and application of a distractor.




*Figs. 105-108.* X-ray of a patient with Crouzon's syndrome during various phases of advancement of the maxilla.

jaw, keeping it connected to the palatine arteries and to the velo-pharyngeal musculature. It is carried out through an intraoral approach with incision of the upper gingival fornix, from one pyramidal apophysis to the other. Via the subperiosteal approach, the antero-lateral wall of the maxilla is exposed up to the pterygoid incisure. Starting from the free edge of the piriform opening, it is possible to proceed with detachment of the floor and the lateral wall of the nasal fossa, reaching to below the inferior turbinate bone. The osteotomic line starts from the piriform opening, continuing horizontally into the antero-lateral wall of the maxillary, and ending up corresponding to the pterygoid incisure. Via the endonasal approach, osteotomy of the lateral wall of the nasal fossa is completed, preserving both the lacrimal duct and the inferior turbinate. Detachment of the maxilla is concluded when the two osteotomies meet along the posterior wall of the upper jaw, taking care to avoid the internal maxillary artery and the posterior palatine arteries. The aim of maxillary advancement is to obtain a first class occlusion. Stabilization of the position gained is guaranteed by use of titanium or reabsorbable plaques.

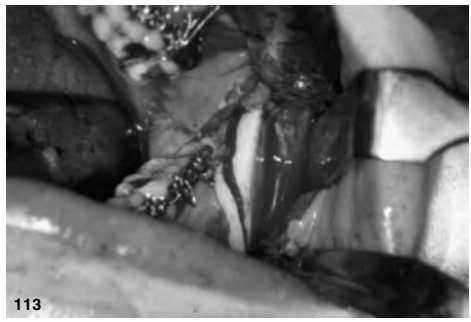



*Figs. 109-111.* Diagram and intraoperative images of Le Fort I maxillary osteotomy.

*Mandibular advancement osteotomies*

Regardless of the type of syndrome, retro-microgenia is responsible for mandibular OSAS.

The classical operation for mandibular advancement is bilateral sagittal osteotomy, according to Obwegeser[27] (Figs. 79, 112, 113), which allows three-dimensional movements of the mandibular body to be achieved, increasing the pharyngeal and oral cavity in order that it accommodates the tongue more easily; moreover, advancement of the chin induces forward displacement of the


*Figs. 112 and 113.* Diagram and intraoperative images of sagittal mandible osteotomy.

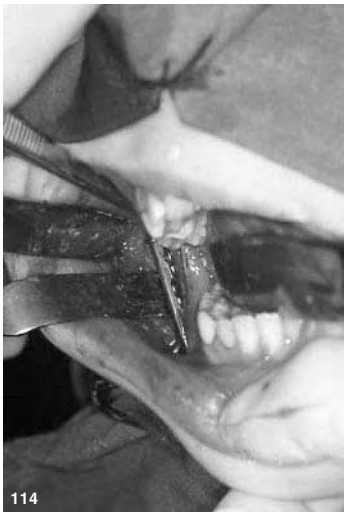
insertion of the geniohyoid and genioglossus muscles, and, at the same time, of the hyoid bone as well, thus increasing the respiratory space. However, this operation is reserved for patients who have finished growing and who already have their second molars. Orthodontic treatment is necessary in order to obtain first class occlusion, instead of the second class characteristic of these patients.

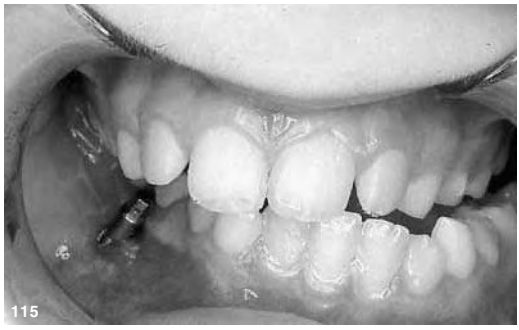
Treatment of mandibular hypoplasias in very young patients is more difficult; it is necessary to bear in mind that the mandible must be helped to resume its growth, and that this starts from the temporo-mandibular joint. Therefore, from the very outset, it is necessary to evaluate the extent of possible articular involvement in the pathological framework.

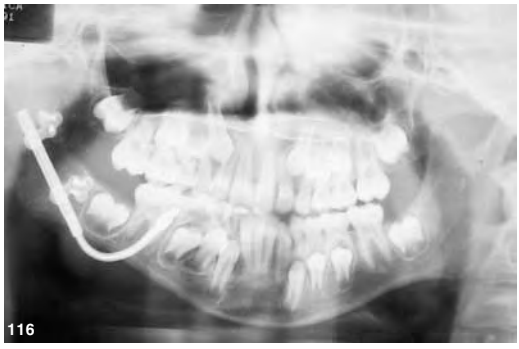
The aim of treatment should be the removal of articular damage wherever possible, at the same time attempting to achieve the best conditions in order that the functional treatment, based on intraoral activators, will be successful.

Over the last few years, the use of bone distractors has been successfully proposed in maxillofacial surgery. This method had already been adopted in orthopedic surgery, clinically applying Ilizarov's experience in lengthening the limbs. The first attempts in the field of maxillofacial surgery were carried out by Snyder *et al.* in 1973 on a dog,[28] but only in 1990 were studies intensified. Since then, many types of distractor have been developed, which now permit more precise movements for the control of vectors of bone lengthening, both for the mandible and the upper maxilla, or for the entire facial complex.

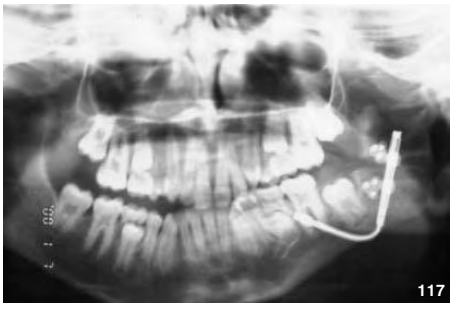
The development of extra- or intra-oral, mono- or multidirectional, mandibular distractors has led to an indisputable advantage in the treatment of patients who are still growing (Figs. 114-116). This technique requires very careful planning, as far as the point at which the distractor should be applied and the choice of the lengthening vector are concerned (Figs. 117-119). It is also necessary to underline the importance of the dimensions of the distractor, which should be proportional to those of the mandible being treated. Regardless of the type of distractor selected, an intraoral approach is used in the surgical technique, with subperiosteal exposure of the mandible, followed by osteotomy, which we personally prefer to be complete, to which the distractor is straddled

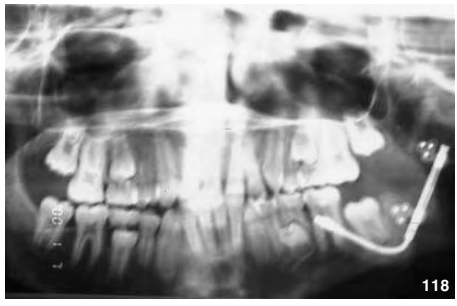


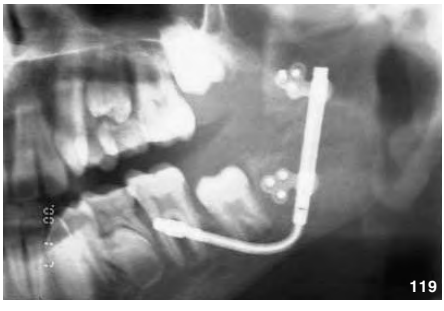




*Figs. 114-116.* Application of an intraoral mandibular distractor: occlusal and X-ray details.




*Figs. 117-119.* X-rays during the lengthening phases of a mandibular ramus.

and fixed with microscrews. Preparation of holes for application of the screws prior to completion of the osteotomy is recommended, in order to simplify fixation of the distractor.

If an extra-oral distractor is used (Fig. 84),[29] the screws are applied transcutaneously with a minimal incision, whenever possible, using some of the incisions already made during elimination of any excess auricular buds.

The distractor is activated while still in the operating theater, in order to obtain initial lengthening, and after a postoperative wait of one week, it is possible to proceed with lengthening at 1 mm/day. Once the planned lengthening has been achieved, the distractor is kept in position for approximately two months before being removed.

Apart from bone lengthening, this technique also offers the advantage of increasing the length and volume of the soft tissues (muscles, vessels, and nerves).

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# THE EFFICIENCY OF ADENOTONSILLECTOMY IN CHILDREN SUFFERING FROM SLEEP APNEA SYNDROME AND SNORING

## A prospective study with pulsoximetric and polysomnographic results

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### Abstract

*Objective:* Adenotonsillectomy (T&A) is one of the most frequently performed pediatric operations. Nevertheless, its efficiency has been repeatedly put into question over the past decades. A prospective study was undertaken to determine the efficiency of T&A in children suffering from snoring and obstructive sleep apnea (OSAS). *Methods:* Eighty children were analyzed prospectively before and after T&A to determine the incidence of snoring and nocturnal obstructive symptoms. The oxygen desaturation index (ODI) was measured in 35 children suspected of having a sleep apnea syndrome. In six of these children, polysomnographic studies were also carried out. *Results:* The obstructive symptoms, especially snoring and respiratory apneas, disappeared or were significantly reduced in 91% of cases after T&A. All preoperatively pathological ODIs and AHIs (apnea/hypopnea index) normalized after the operation ($p < 0.005$). *Conclusion:* Adenotonsillectomy is the operation of choice for treating pediatric OSAS.

### Introduction

Almost no other operation has resulted in as much controversy over the past decades as adenotonsillectomy (T&A). Nevertheless, it remains one of the most frequently performed pediatric operations. Recurrent tonsillitis is the most frequent indication for T&A.[1] However, obstructive sleep apnea syndrome (OSAS) is becoming one of the most important indications at many centers for performing T&A.[2]

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We carried out a prospective study to determine the efficiency of T&A for treating snoring and OSAS in children.

## Methods

T&A was performed on 80 children at the University Clinic for ENT, Head and Neck Surgery at the University Hospital, Berne, Switzerland in 1998. Ages ranged between one and a half and 14 years (mean 6.2 ± 3 years). With the exception of two children (3%), T&A was performed without complications. A questionnaire to be completed by parents before and after surgery, and which was designed at our institution, recorded respiratory apneas, nocturnal snoring, nocturnal dyspnea, and frequency of waking during sleep.

Preoperatively, we checked the clinical ENT status and carried out blood tests and body measurements. In addition, nocturnal oxygen saturation was measured on an outpatient basis before T&A and between six and 12 months afterwards in 35 children suspected of having OSAS, using transcutaneous pulse oximetry. Nocturnal polysomnography was carried out pre- and postoperatively in six of these children as inpatients in the Sleep Laboratory.

## Results

Snoring was noted in almost all the children prior to T&A, and as often as every night in 62 children (78%). Six to 12 months after the operation, snoring had disappeared in 58 children (73%), and only occurred occasionally in 21 children (24%). Snoring continued unchanged in only six children (8%). The nocturnal respiratory standstill observed preoperatively in 51% of the children, and the waking at night because of this in 30% of the children, were only noted postoperatively in a single case. The ODI of 35 children was pathological in 12 before T&A (10.4 ± 3.8). Similarly to Stradling,[3] at our institution, up to five desaturations per hour were regarded as a normal value. All these values normalized after surgery, as can be seen in Figure 1. Before the operation, the apnea-hypopnea index (AHI) yielded highly pathological values of 13.9 ± 7.3 (normal ≤5) in four children on polysomnography. Six months after T&A, all values had dropped to normal (Fig. 2).

## Discussion

These days, OSAS has become an important indication for T&A in children. Various studies show that pediatric OSAS can be successfully cured with T&A, and that the consequences resulting from OSAS, such as cor pulmonale, pulmonary arterial and systemic hypertension, hyposomnia and neurocognitive changes, can

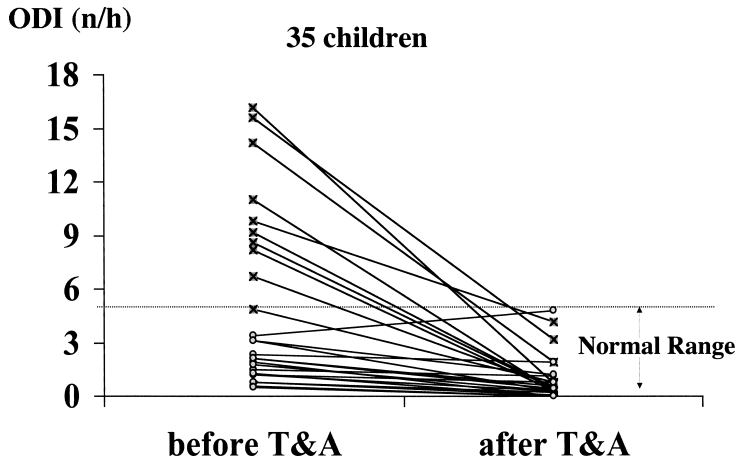


*Fig. 1.* ODI measured with pulse oximetry before and six months after T&A in 35 children with snoring and sleep apnea.

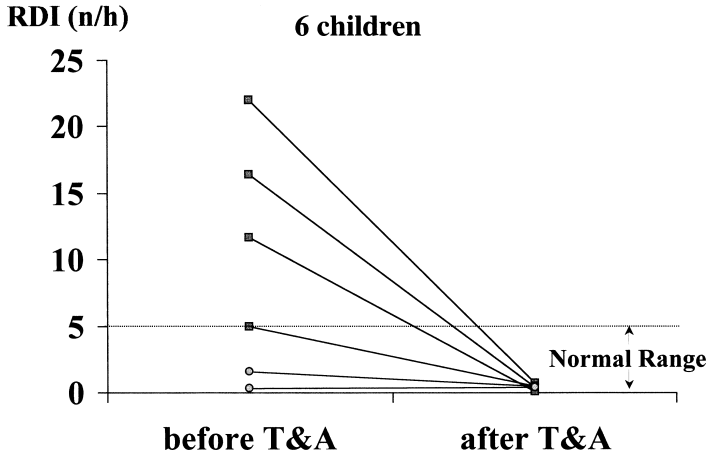


*Fig. 2.* Polysomnographically measured AHI or respiratory disturbance index (RDI) in six children before and six months after T&A.

be prevented successfully.[4-9] However, it is not always easy to diagnose OSAS. A history of snoring and respiratory standstill, together with the clinical findings of large tonsils and adenoids, are not always enough for a reliable diagnosis.[10-12] The fact that almost 10% of four- to six-year-old children are habitual snorers but otherwise completely healthy, and the finding that small tonsils or the absence of adenoids do not rule out the possibility of OSAS, make the diagnosis of OSAS more difficult.[13,14]

All the 80 children in this study were habitual snorers prior to T&A, but only 35 children were suspected of having obstructive symptoms. Of these, a diagnosis of

OSAS was confirmed either with polysomnography or pulsoximetry in 14 cases.

If a diagnosis of sleep apnea syndrome (SAS) is not very clear on the basis of history and clinical findings, additional objective confirmation is recommended before T&A is performed. Polysomnography is still the gold standard for this purpose. It allows accurate identification of the cause of hypoxemia, differentiation between peripheral and central SAS, and the detection of other sleep disorders.[15] The disadvantage of this investigation is the considerable effort and expense involved. However, awareness of the existence of severe OSAS is also important for the surgeon, in order to be able to estimate the risk of potential postoperative complications correctly.[9] One alternative to polysomnography is nocturnal pulse oximetry on an outpatient basis. This is an economical, patient-friendly method of recording oxygen saturation drops. The main disadvantages are the inability to record arousals, and to distinguish between central and peripheral SAS. The sensitivity of pulse oximetry for recording OSAS is relatively high (generally over 80% in the literature), but the specificity is only 50-60%.[16,17] The desaturation index is defined as the number of oxygen drops of more than 4% per hour. No global consent has yet been reached regarding a normal value for nocturnal pulse oximetry.

According to the studies performed by Stradling[3] for the evaluation of nocturnal oxygen saturation, an ODI of >5 is assessed as pathological. Of our 35 children subjected to pulse oximetry investigations, 12 exhibited pathological values. Considering the restrictions of pulse oximetry described above, it is possible that, in our study, OSAS children were incorrectly classified as benign snorers. The polysomnographic criteria for the diagnosis of OSAS in adults cannot be applied to children and had to be specially adapted.[18,19] The AHI is considered to be one of the most important parameters. In polysomnographic studies, an AHI greater than 10 is generally pathological in adults, but several studies have shown that this value is too high for children and that even an AHI >1 may already have pathological significance.[19] The normal range at our institution is an AHI of up to 5. Four children had pathological AHI values.

The pulse oximetry investigations carried out at the same time showed that oxygen saturation drops are not necessarily seen in OSAS patients. Only a single patient with OSAS was found to have a pathological ODI. In our study, T&A resulted in normalization of all values for pulse oximetry and for polysomnography (Figs. 1 and 2). In most pediatric cases, T&A cures SAS, except in children with craniofacial abnormalities and in children with a central or mixed SAS.

## Conclusions

The present study confirms that T&A in children cures OSAS and significantly reduces snoring. This was confirmed not only from observation of the clinical history, but also from objective observation, such as pulsoximetry and polysomnography measurements.

In this context, nocturnal pulsoximetry for recording SAS has proved to be a non-invasive, simple screening method which can be performed on an outpatient basis. However, SAS cannot be definitively ruled out solely on the basis of normal pulse oximetry. The method of choice for the reliable diagnosis of OSAS is still polysomnography.

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# ADULT AND PEDIATRIC COBLATION TONSILLECTOMY

## Double-blind randomized controlled studies and complication rates in 800 patients

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### Introduction

Tonsillectomy remains a very common operation for otolaryngologists, whether it is done for recurrent infection or for the relief of airway problems, including snoring and obstructive sleep apnea syndrome. Many different techniques have evolved over the years, each with its own advantages and disadvantages.

The following pages describe our experience in Blackburn, with an exciting new technique called coblation tonsillectomy, which we have developed and found to have distinct advantages in terms of ease of use, reduced postoperative pain and morbidity, and low rates of early and delayed hemorrhage. We have used this technique in over 800 cases and are convinced that it is the method of choice for tonsil removal.

### Technology

Coblation surgery involves the use of a disposable handpiece or wand, connected to a control unit and operated by foot controls. A radiofrequency bipolar current is conducted across the electrodes at the tip of the wand. This activates normal saline solution delivered through the wand to create a plasma field of sodium ions at the tip. This plasma field dissolves intercellular bonds at a temperature of 60-70°C. Disintegrated tissue and saline are aspirated from the operative field by suction built into the wand itself.

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## Techniques

There are two ways of removing the tonsil. Coblation tonsillotomy involves volumetric removal of lymphoid tissue, layer by layer, until the first sign of muscle fibers can be seen through the tonsil capsule. This method is suitable for cases where less than 100% removal of tonsil tissue is acceptable, as in airway obstruction. Coblation tonsillectomy uses the wand as a dissection tool working in the peri-tonsillar plane. This method is suitable for both airway obstruction and infection cases. Anecdotal evidence suggests that the first method is the less painful, but takes an extra five to ten minutes in theater. Almost all our patients undergo complete tonsillectomy.

The ENTec Evac 70 wand is used in all cases. Surgery had been carried out in the USA with a different ENTec wand called a Plasma scalpel and with the pharynx completely filled with saline solution.[1] This method did not appeal to this author, but the production of the Evac wand allowed our method of coblation tonsillectomy to emerge as a very practical and viable technique.

General anesthesia is used in all cases. Endotracheal intubation is most commonly used, although laryngeal mask anesthesia is also acceptable. The Coblator unit is adjusted to a power level of six, which has been found to be the best compromise between cutting and coagulating properties. A saline flow of two to three drips per second is adequate. The tonsil is grasped with forceps and drawn medially, and the peritonsillar space is opened gradually by smooth stroking of the wand from the lower to upper poles. As the tonsil peels from its bed, vessels will be seen to blanch and dissolve, together with fibers of the peritonsillar areolar tissue. If a vessel does bleed, it is identified accurately as the saline washes away any blood, and the coagulation pedal on the foot control is depressed for two to three seconds in order to achieve hemostasis. Performed in this way, pediatric tonsillectomy takes approximately three minutes per side and adults take perhaps an extra two minutes per side on average.

There is a learning curve, with children being much easier initially, and for this reason it is suggested that thorough experience is gained in pediatric cases before moving on to adults. Any difficulties encountered are generally a result of rushed operator technique rather than any weakness in the technology.

Performed as described, coblation tonsillectomy is a fast, bloodless and pleasing operation.

A number of post-quinsy tonsillectomies have been performed in our department without any additional problems being seen. The device dissolves the scarred fibrous attachments to the tonsillar fossa efficiently and without using physical force.

## Trials

Two randomized, prospective, double-blind, controlled trials of coblation tonsillectomy versus conventional dissection and diathermy were carried out in our department, in adult[2] and pediatric groups.[3]

*Pediatric trial*

*Material and methods*

Thirty-eight children were studied: 18 underwent coblation tonsillectomy and 20 had tonsillectomy by dissection with bipolar diathermy hemostasis. Patients were prospectively randomized to either one method or the other. Parents were given a chart on which to record daily pain scores on a visual analog scale and whether or not normal dietary intake was achieved. Patients were reviewed on Day 9 in order to collect pain charts and to assess healing of the tonsillar fossae. Neither parents nor the examining doctor were aware of the operative method used. Ages ranged from four to 12 years. All patients were discharged from hospital on the same day as surgery.

*Results*

Figure 1 shows the mean daily pain scores for the two groups of patients. The differences are visually dramatic, and statistical analysis showed a highly significant difference between the two groups ($p < 0.0001$).

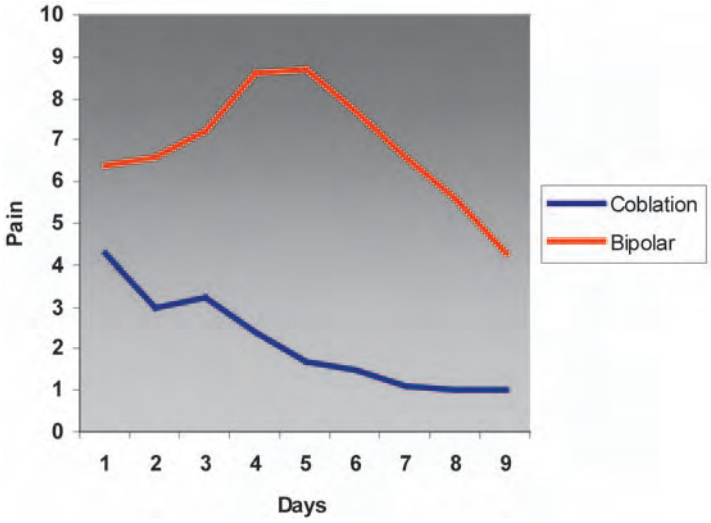


*Fig. 1.* Pediatric tonsillectomy pain comparison.

The average day of return to a normal diet was 2.4 for the coblation group and 7.6 for the dissection group ($p < 0.0001$: significant). A difference in healing was also noted. At nine days, all the fossae of the coblation group were free of slough, but all the dissection and diathermy patients still had considerable slough present in their tonsillar fossae. There were no cases of reactionary or secondary hemorrhage in this study.

*Adult trial*

*Material and methods*

Ten patients took part in this study. In each case, one tonsil was removed by dissection and bipolar hemostasis and the other by coblation dissection. This was randomized prospectively. All patients were treated as day cases. Each patient was given a chart on which to record daily pain scores on a visual analog scale. They were reviewed after nine days by a doctor who did not know which side had been treated by which method. Pain scores were collected, and the appearance of the tonsillar fossae on each side was recorded in terms of how much slough was present.

*Results*

The results were compared by non-parametric methods using Wilcoxon's matched pairs signed ranks test. Coblation tonsillectomy was consistently less painful than the standard dissection method.

Figure 2 shows the mean daily pain scores for both sides.

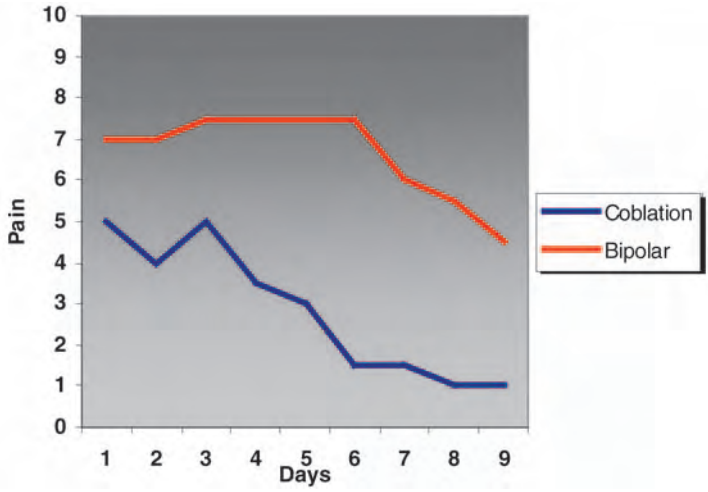


*Fig. 2.* Adult tonsillectomy pain comparison.

The differences between pain scores on each postoperative day for each side were statistically significant ($p < 0.002$). Significant differences in the amounts of slough present in the dissection and the coblation sides were also demonstrated ($p < 0.001$; Table 1). There were no postoperative complications in this study group.

*Table 1.* Area of slough in each tonsillar fossa (0% totally healed, 100% covered in slough)

| *Coblation (%)* | *Bipolar (%)* |
|---|---|
| 0 | 50 |
| 50 | 100 |
| 0 | 100 |
| 0 | 100 |
| 0 | 100 |
| 0 | 100 |
| 25 | 100 |
| 25 | 100 |
| 0 | 100 |
| 0 | 100 |

## *Discussion*

These trials indicate that coblation tonsillectomy produces significantly less postoperative pain, and this subsides more quickly than dissection tonsillectomy with bipolar hemostasis.

Although no attempt was made accurately to measure analgesia consumption, anecdotally painkillers are seen to be used for a shorter time in coblation patients. Some of the mothers of the pediatric patients returned cartons of painkillers unopened. Clearly, a study measuring analgesic consumption would be useful.

The results in the pediatric study also showed a more rapid return to a normal diet, which was statistically significant. This has implications in terms of minimizing infection and subsequent secondary hemorrhage.

Having demonstrated a reduction in postoperative pain levels in both adults and children for this technique, we have adopted it as our method of choice for tonsillectomy in Blackburn.

This policy coincided with a disturbing development regarding tonsillectomy in the UK. The emergence of new variant CJD in our young adult population, and the knowledge that the responsible prion can be concentrated in lymphoid tissue prompted the UK government to introduce a policy of only using disposable tonsillectomy instruments.[4]

In our department, we spent a proportion of the money provided by the government for disposable instruments on coblation wands. This enabled us to gather substantial data on the postoperative hemorrhage rates for this procedure. Clearly a new operative technique would not be acceptable if its hemorrhage rates were higher than those of other methods, regardless of its other advantages.

## Hemorrhage rates for coblation tonsillectomy

### *Material and methods*

The reactionary and secondary hemorrhage rates for the last 789 coblation tonsillectomies carried out in our department are presented here. These are compared with a similar number of dissection tonsillectomies also carried out in our department. The coblation group is divided into 485 children and 304 adults. The indication for surgery was recurrent infective tonsillitis in over 90% of cases, with airway obstruction and snoring accounting for the remainder. Patients were told to return to the ENT ward if any bleeding was seen in the postoperative period, and all such patients were admitted for overnight observation and any other necessary treatment. The same advice was given, and the same admission policy maintained, regardless of operative method used. For this reason we believe that our detection and recording of secondary hemorrhage has been accurate.

### *Results*

The rates of reactionary hemorrhage in all groups was under 1%, and there was no statistical difference between coblation and dissection. With such a low incidence, it would require a study of thousands of patients before any conclusions could be drawn.

In the case of secondary hemorrhage, there was a clear difference between coblation and dissection with bipolar hemostasis. The most dramatic difference was in the pediatric group in which secondary bleeding was six times more common in the dissection group (Table 2, Figs. 3 and 4).

*Table 2.* Secondary hemorrhage rates

| | *Dissection (%)* | *Coblation (%)* |
|---|---|---|
| Children | 4.97 | 0.82 |
| Adults | 8.29 | 4.6 |
| Combined | 6.18 | 2.28 |

### *Discussion*

We cannot be certain why coblation patients have a lower secondary hemorrhage rate than the standard technique. However, it is likely to be related to the efficient initial hemostasis with the equipment. The fact that this is achieved without causing any significant thermal damage or the type of crush injury involved in using ties, goes some way to explaining the reduced levels of pain

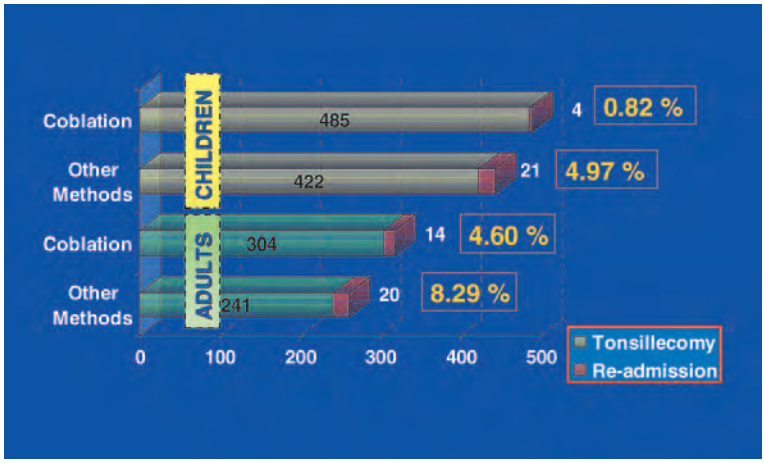


*Fig. 3.* Secondary hemorrhage rates – adults and children.

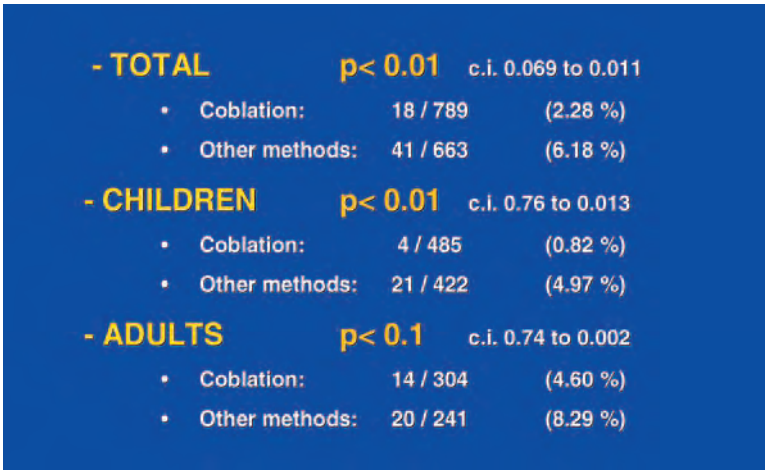


*Fig. 4.* Secondary hemorrhage rates – statistic analysis.

and better dietary intake seen after coblation tonsillectomy. These factors probably result in a lower level of infection in the tonsillar beds, which is generally considered to be the main cause of secondary bleeding.

Although this is largely speculative, there is laboratory evidence of reduced collateral damage comparing this technology to monopolar electrosurgery.[5]

## Conclusions

Radiofrequency technology has an established place in the treatment of snoring and sleep apnea, by direct treatment of the soft palate. Relief of the effects

of tonsil hypertrophy often has an important role to play in addition to palatal surgery. The most effective approach must be total or near total removal of the tonsils. This adds to the morbidity of the treatment and any method of limiting postoperative pain and secondary hemorrhage rates is worthy of serious consideration. The studies described above have demonstrated significant advantages in terms of reduced pain levels, rate of healing and return to normal diet, and reduced secondary hemorrhage rates with coblation tonsillectomy.

While consideration must be given to the costs of the disposable wands, this may well be outweighed by the saving in readmissions for secondary bleeding, which has its own financial implications.

It is a very different technique from traditional dissection and must be performed with care and a gentle touch. Certainly, junior staff in our own department and colleagues from elsewhere, who have learnt this technique, now see tonsillectomy in a new light.

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# RESULTS OF THE TREATMENT OF OBSTRUCTIVE SLEEP APNEA SYNDROME IN CHILDREN

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## Introduction

Many malformative, inflammatory and, more rarely, neoplastic diseases cause obstructive sleep disorders in children, but adenotonsillar hyperplasia is undoubtedly the most common etiological agent in polymorphic nocturnal clinical symptoms ranging from snoring to obstructive sleep apnea syndrome (OSAS). It is common knowledge that children with airway obstruction almost always snore during sleep; snoring is often loud and breathing irregular, because of long respiratory pauses, defined as apneas when longer than ten seconds, due to complete oropharyngeal obstruction during sleep. Long and frequent apneas may have progressive serious effects on psychophysical growth and on the cardiovascular and nervous system, and may sometimes even lead to death (sudden infant death syndrome, SIDS). Most authors agree on the necessity to remove occlusions of the upper respiratory airways by tonsillectomy and/or adenotomy, which can generally resolve both the apneic syndrome and the relative complications.[1]

Our experience confirms the data in the literature regarding the role of adenotonsillar hyperplasia on the pathogenesis of the syndrome, which has become more and more frequent in Italy over the last few years, probably in relationship with the progressive reduction of adenotonsillectomies for phlogistic indications. In almost all cases, after surgery we observed a quick and sometimes complete improvement in ronchopathy and OSAS. In only a few cases did we observe the return of respiratory alterations during sleep, after an initial period of well-being. Therefore, according to some authors,[2-4] the benefits of occlusion surgery should be evaluated by means of a long follow-up, in view of the continuous evolution during pediatric age of osteomuscular and lymphatic structures, which could alter the initial results positively or negatively. Therefore, the aim of our research was to study the postsurgical clinical evolution of sleep obstructive pathology in order to verify, over a fairly long

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observation period, the causes of eventual failures, and to see whether they are linked to surgical problems or to problems unrelated to upper airway obstructions.

## Material and methods

We examined 38 children (22 males and 16 females), with ages ranging from 18 months to seven years, affected by OSAS due to tonsillar and/or adenoid hypertrophy. In relation to the place of the obstruction, we performed adenectomy in six cases, tonsillectomy in 20 cases and adenotonsillectomy in 12 cases. Postsurgical evaluation was carried out after four months and after one year. In the follow-up, we considered the sleep disorders obtained directly from the children's parents and from polysomnographic data. Children who, in the preoperative tests, showed blood and cardiopulmonary alterations, were submitted to hematological, radiological, electro- and echocardiographic controls. When no improvement in sleep disorders could be seen four months after surgery in patients having undergone the partial operation (tonsillectomy or adenotomy), we removed the residual structures, which were probably responsible for the OSAS pathogenesis.

## Results

### *Preoperative data*

All the children had typical signs and symptoms of OSAS: very loud nocturnal snoring with at least 30 apneas lasting for more than ten seconds during seven hours of sleep. Sleep quality was obviously altered in all cases, with frequent arousals, pavor nocturnus, enuresis and hypersomnolence and, more often, daytime irritability. In all cases we also observed severe alterations in the blood, with evident polycythemia in three children. In two cases there were severe cardiopulmonary pathologies with right ventricular overload (ventricular dilatation and hypertrophy) in one patient and biventricular hypertrophy in the other. Chest radiography showed a pulmonary pathology in five patients due to pulmonary hypertension, which usually characterizes the most severe cases.

### *Postoperative data*

*Four-month follow-up*
*Snoring:* Complete resolution of snoring was observed in 18 children (48%) and a considerable improvement in ten (26%); no improvement was seen in ten cases, four of whom still had apneas. In two cases of snoring without apneas, a neurological assessment pointed to severe muscular hypotonia.

*Apnea:* Apnea was no longer evident in 35 of 38 cases (90%). There was complete resolution in all cases of tonsillectomy, while in three of six cases of adenotomy, the length and frequency of apneas did not change. A residual alteration of blood (>$pCO_2$ and pathological hemochrome) was still present in only one patient (corresponding to the case of severe OSAS after adenotomy). The electro- and echocardiographic tests carried out in two patients with severe cardiac dysfunction preoperatively, showed rather complete resolution in one patient, while in the patient with previous biventricular hypertrophy, we only observed a slight improvement of cardiac function with partial reduction of ventricular volume. In five children who had bronchopulmonary infections preoperatively, clinical examination and radiological controls showed complete resolution of the pathology.

*One-year follow-up*

In 19 of 20 patients who had undergone tonsillectomy, we could still observe normal sleep; in one case, after initial improvement, a gradual return to severe OSAS occurred, and adenotomy was performed without delay. In three cases who had undergone adenotomy and who had residual OSAS at a previous control, no improvement could be documented at one year; we therefore proposed tonsillectomy, which was refused by the parents of one case. With regard to cardiac evaluation in the patient affected by dilatative cardiopathy, one year after surgery, pathological signs were still present with only a slight improvement compared to the previous situation (Table 1).

*Table 1.* One-year follow-up results

| *Symptom* | *Presurgically* | *Postsurgically* | | |
|---|---|---|---|---|
| | | *four months* | *one year* | *after second operation* |
| Snoring | present (100%) | absent (18 cases: 48%) improved (10 cases: 26%) present (10 cases: 26%) | absent (38 cases: 100%) | absent (38 cases: 100%) |
| Apneas | present (100%) | absent (34 cases:90%) present (4 cases: 10%) | present (4 cases: 10%) | absent (37 cases: 100%) |
| Cardiovascular alterations | one right ventricular overload<br>one biventricular hypertrophy | biventricular hypertrophy | partial resolution of hypertrophy | still biventricular hypertrophy |
| Pulmonary alterations | five parenchymal densification | absent | absent | absent |

*Follow-up after second operation*
Second operations (in the case of adenotomies and in two cases of tonsillectomy) led to complete resolution of the syndrome.

## Discussion

In agreement with articles in the literature, our research has confirmed the importance of removing any obstacle in the upper airways (particularly hypertrophic tonsils and adenoids) in children affected by OSAS. In fact, after surgery, we obtained the complete resolution of apneas (90% after the first operation, 10% after the second) in all subjects. The results were not as good with regard to ronchopathy, especially when compared to the improvements obtained in the apneic syndrome; in some cases we observed complete resolution of apneas, but with persistence or only partial improvement of snoring. It is probable that, in the pathogenesis of snoring, an important role is played by muscular hypotonia of the oropharyngeal musculature (constrictor, lingual and palatal muscles), which characterizes the pediatric age, particularly in lymphatic subjects. In fact, in two cases of persistent snoring, neurological tests showed a general muscular hypotonia, which was probably responsible for the sleep disorders. We also observed that, even if the resolution of apnea was already evident immediately after the operation, the improvement in snoring was often gradual, especially after tonsillectomy. This could be explained by the progressive widening of the oral cavity as a result of cicatricial retraction of the peritonsillar structure. The postsurgical follow-up, lasting for at least one year, gave us an indication of the best therapeutical practice, and most importantly of the advantages gained from performing the operation early, despite the higher anesthesiology risks in very young children; in fact, well-timed surgery can avoid severe cardiopulmonary complications, which can sometimes be irreversible (as in one of our patients), or SIDS.[5,6] In our opinion, long-term follow-up after surgery is very important: very frequently, some symptoms improve or even disappear almost immediately, but in some cases, after a few months, we observe the reappearance of rather to very severe apneas and/or snoring. Above all, this can be explained by some failure in the obstruction surgery; in fact, in our experience, apnea and/or snoring may reappear in patients only treated with tonsillectomy or adenotomy, while adenotonsillectomy quickly resolves the symptoms connected with OSAS in all cases. In our patients, an indication for adenotomy alone was given in only a small percentage of cases (six patients: 16%), three of whom did not benefit from the surgical operation. Some researchers identify the rhinopharyngeal obstruction as being the only cause of OSAS[7-11]. According to their hypothesis, during sleep, oropharyngeal air flow resistance is greater than nasal, and therefore oral breathing increases the negative pressures in the upper airways. Consequently, this oropharyngeal obstruction causes the collapse of the pharyngeal walls and the apneas.

However, it is evident from our study that, in pediatric age, rhinopharyngeal obstruction does not play as decisive a role in the pathogenesis of the syndrome as oropharyngeal obstruction due to tonsillar hypertrophy. Moreover, when there is no evident obstructive factor, before performing adenotomy, it is necessary to check for a possible velopharyngeal muscular hypotonia as a concomitant cause of the sleep disorder. Yet, in our study, this hypothesis only explains the return of apnea after tonsillectomy performed in the patient with obstructive tonsillar hypertrophy without evident nasal obstruction. In fact, we too can argue that, in this case, there was enhancement of the adenoids after tonsillectomy, as a consequence of repeated rhinopharyngeal phlogosis; and so the nasal obstruction may well have had an important pathogenetic role in the syndrome. This can be proved by prompt recovery after adenotomy.

In conclusion, our study confirms the necessity to establish preoperatively the most important place of the obstruction using all the tests compatible with the age of the child (clinical examination, rhinomanometry, radiography, etc.). In cases of doubt, we prefer to perform an adenotonsillectomy in order to avoid a protracted functional alteration which would only put the cardiopulmonary apparatus at risk, as well as to avoid the not so remote risk of having to perform a second operation shortly after the first.

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# OUT-PATIENT TREATMENT OF SNORING AND SLEEP APNEA SYNDROME WITH $CO_2$ LASER-ASSISTED UVULOPALATOPLASTY

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## Introduction

Laser-assisted uvulopalatoplasty (LAUP) is a technique using local anesthesia for the treatment of snoring, upper airway resistance syndrome (UARS), and mild to moderate obstructive sleep apnea syndrome (OSAS) in an office setting.

## Indications

Having completed a medical history questionnaire, the patient is examined by the surgeon for a diagnosis. A flexible fiberoptic nasopharyngolaryngoscope is used to evaluate the upper airway and to refine the selection of the LAUP candidate. The patient is asked to breathe normally through the nose and to swallow, in order that nasopharyngeal closure can be observed. Then he is asked to snort voluntarily for the vibrations of the velum to be observed. This fiberoptic evaluation helps any site that is collapsing at the velopharynx or at the tongue base level to be detected. The palatine and lingual tonsils are also examined, as well as the size and position of the tongue base. Patients who do not demonstrate an open vallecular space are considered poor candidates for LAUP, as the obstruction at the hypopharynx level cannot be improved with palatal surgery.

When OSAS is suspected, a full-night of polysomnography is very important in order to assess its presence and severity. X-ray cephalometry, or CT scan of the head, are also carried out if necessary.

It has been shown that the majority of snorers benefit from LAUP, a new technique carried out under local anesthesia, introduced by Kamami in the late 1980s,[1-3] and popularized in the USA in 1992 by Coleman *et al.*,[4,5] Krespi *et al.*[6] and Walker *et al.*[7] Many authors from all over the world have already

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published their results with this technique.[8-11] LAUP is designed to correct upper airway obstructions and soft tissue vibrations at the level of the soft palate, by reshaping and stiffening the tissues of the soft palate.

## Contraindications

LAUP is contraindicated in snoring caused by conditions such as severe OSAS (apnea-hypopnea index (AHI) greater than 30), and serious nasal or maxillo-facial problems (trismus, submucous cleft of the palate). Caution must be taken in treating some patients who use the uvula extensively in their native language (Arabic, Russian, German, Hebrew, and Farsi), who practice sea-diving or play wind instruments.

In cases of OSAS, LAUP is mainly indicated in mild and moderate cases. However, it also plays a role in patients with severe OSAS who do not respond to continuous positive air pressure (CPAP), by increasing tolerance and reducing the pressure required to open the upper airway wider.

## Description of the procedure

LAUP is performed with a $CO_2$ laser, with the patient seated in an upright position. Depending on the thickness of tissue to be incised, the power is set at 20-40 watts, in the continuous mode. A specific handpiece is used with a spot size of 0.6-3.5 mm, and a focus of 300 mm. This handpiece has a focus-defocus ring: focus to cut, and defocus to coagulate. The patient is premedicated with an oral analgesic, Vitamin K1, and anti-emetic, and his blood pressure is checked. The patient and staff are required to wear special protective laser goggles. Laser safety rules are followed. Breathing instructions are given to the patient: inhale slowly and deeply and then exhale slowly. These instructions are very important as the laser can only be activated during slow exhalation, in order to avoid inhalation of the plume. Local anesthesia is then administered using a 20% benzocaine (Ceticaine) sprayed over the soft palate and uvula, followed by an injection of a 1-2 ml mixture of 2% lidocaine with 1:100,000 epinephrine bilaterally into the base of the uvula.

This technique is designed to remove the minimum amount of tissue consistent with the reduction of snoring. This conservative approach to tissue removal eliminates the development of velopalatal insufficiency as a complication of LAUP.

The first step is to debulk the lower part of the uvula, from left to right, immediately after infiltration of the local anesthetic. Then, two paramedian full thickness, through-and-through ‘trenches’ are made over the soft palate, on either side of the uvula, to a height of about 1-2 cm. These trenches are created with a backstop handpiece in order to prevent hitting the back of the

throat, lateral to the root of the uvula, and they extend superiorly up to the junction of the soft and hard palate, the 'dimple point'. The tissues of the free edges of the velum are spread open, and the incision looks like an inverted 'U'. Reshaping of 70-80% of the uvula at the apex of the soft palate is carried out, resulting in a small 'new uvula'. A 'new uvula' is created, with further trimming of the inferior and lateral sides of the uvula, from the tip upwards. Its anterior and posterior sides must be preserved, leaving the mucosa intact in order to prevent granuloma formation and facilitate re-epithelialization. This 'new uvula' hangs from the rear of the hard palate, preventing centripetal scar fibrosis, because of the specific make-up of its muscle fibers (which seem to be different from non-snorers). It contains a portion of the azygous muscle which can still contract and prevent velo-palatal insufficiency from occurring. It is similar to a middle pillar in the center of a church vault, supporting the palatine arch, flanked by the lateral anterior and posterior pillars. The main mast of the uvula is masked by the palatostaphylin or uvula azygous muscle, a little spindle-shaped, vertical muscle, entirely enclosed in the velum:[5] its main action is to raise the uvula, and this muscle is only attached to the posterior side of the hard palate at its upper edge. So it is very important partially to preserve this main mast as a support for the middle of the velum. The procedure reaches its conclusion when the patient can no longer make a snorting sound.

Using the 'Surgitouch' flashscanner produces minimal charring, while ablating the tissue rapidly and bloodlessly (the Surgitouch can adequately coagulate small diameter vessels encountered), and facilitates proper healing. When applied to the area of incision, the slightly defocused beam adequately controls bleeding from any area which is still bleeding after the incision has been made. No sutures are required.

A pharyngeal handpiece specifically designed for this procedure incorporates a 'backstop' and a smoke evacuator. Smoke is evacuated by a high-speed, dedicated laser evacuation system, which is connected to the laser handpiece. The backstop shields and protects the lateral and posterior pharyngeal wall, and the smoke evacuator maintains clear visibility in the operative field during the operation, providing full patient comfort and avoiding nausea and coughing. The tongue base is depressed inferiorly with a wet wooden tongue depressor.

To repeat, the $CO_2$ laser can be used in two ways: with the focused beam as a 'light knife' for performing hemostatic incisions of the velum, or with the Surgitouch for ablative char-free vaporization to debulk tissue. With the laser, it is possible to gain access to areas of the oral cavity which are difficult to reach. Light bleeding may occur during the procedure, but it is easily controlled using the defocused mode of the laser or the radiofrequency bipolar electrode, on both sides of the new uvula, if necessary.

Finally, prior to terminating the operation, the surgeon injects 1 ml of analgesic drug (Ketoprofen) mixed with lidocaine 2% epinephrine, into the top of

the soft palate. This mixture has a delayed action on throat pain, lasting for six to ten days. This postoperative pain-killer injection reduces the "worst sore throat you have ever had", described by some patients after LAUP, to only a slight sore throat, making it easier to tolerate (about twice as less painful on the Analogical Evaluation Scale). If necessary, hemostasis is performed with a radiofrequency bipolar electrode on both sides of the new uvula. This radiofrequency treatment is also useful because its permits better stiffness of the new uvula, with much less vibration remaining.

Immediately after the procedure, the patients are made to gargle with cold water in order to 'wash out' the topical anesthetic, and then to try to swallow with caution.

In OSAS patients, the uvula is usually thicker and longer than in patients with simple snoring. Therefore, the operation takes longer in apneic snorers than in non-apneic snorers, because of the time needed to transfix and trim the uvula.

## Additional procedures

If there is hypertrophy of the pharyngeal or lingual tonsils, it is possible to perform laser-assisted tonsil ablation, with either a fixed 90° or an adjustable front surface mirror handpiece, which permits the laser beam to be redirected in order to hit the pharyngeal tonsils or the posterior third of the tongue. Continuous power and a local anesthetic spray are used. Palatine or lingual tonsillar hypertrophy is treated with the Surgitouch if the size of the tonsils is contributing to OSAS by obstructing the oropharynx.

In cases of nasal obstruction caused by turbinate hypertrophy or septal deviation, a $CO_2$ laser-assisted partial inferior turbinectomy (LAPT) or a septoplasty (LAOS) may have to be performed. In fact, most patients have a LAPTOS (LAPT+ LAOS) before or after the LAUP procedure in order to ensure better nasopharyngeal ventilation.

In some cases, before laser surgery, patients have already had one or two sessions of radiofrequency tissue volume reduction, on the soft palate, with an electrode applied to the soft palate, but without the desired results on snoring. In these cases, following radiofrequency, LAUP is more difficult, with more bleeding and laser penetration into the soft palate being more problematic. In other cases, two years after the initial successful radiofrequency treatment, there is a recurrence of snoring, and patients opt for LAUP because of its good long-term results.

## Postoperative instructions

Immediately after each laser session, most patients are able to return to work or to go home. Voice is unaffected. After the procedure, the patients are given

a prescription for a course of approximately ten days, including analgesics (acetaminophens, acetaminophen with codeine, or paracetamol with codeine), steroids, hydrogen peroxide, and water gargles (to prevent the rare risk of post-operative bleeding), topical anesthetic throat lozenges, anesthetic mouth sprays, and viscous lidocaine to relieve throat pain. They are instructed to avoid drinking alcohol, eating spicy food with vinegar, lemon or spices, and taking aspirin for ten days after the operation.

## Complications and side-effects

The intensity of the postoperative pain and the results on snoring are evaluated with the Analogical Evaluation Scales. Daytime sleepiness is evaluated with the Epworth scale (pre- and postoperatively).

Patients usually complain of moderate to severe 'pain on swallowing', similar to a 'sore throat' for about ten days. Pain intensity reaches its peak three to five days postoperatively, but does not inhibit eating or drinking, speaking or working immediately afterwards. Rarely, delayed bleeding can occur, either during the first 48 hours or approximately eight days after the session, but can easily be stopped in minutes with peroxide and water gargles or silver nitrate. A few patients may complain of a thick, 'dry mucus' sensation, or of a 'foreign body' stuck to the back of the throat; this usually resolves within two to three months. Rarely, oral candidiasis or vaso-vagal reactions occur after injection of the local anesthetic into the palate. Some patients may lose weight immediately after the operation, but the majority of them quickly regain this.

No serious complications have been reported during the operation or the postoperative phase after LAUP: no nasal regurgitation or voice/resonance changes. No clinically identifiable changes in speech or velopharyngeal function, and no stenosis causing narrowing of the nasopharyngeal aperture have been observed, as been seen after uvulopalatoplasty (UPPP). Infection is rare except for occasional oral candidiasis, which can be treated with oral antifungal agents. Postoperative observation in a medical care unit is unnecessary.

## Sleep apnea syndrome patients

Patients with an Epworth scale of up to 10 or a specific anatomy, must undergo pre- and postoperative evaluation by polysomnography. This is performed to show evidence of repeated obstructive respiratory events during sleep on presurgical polysomnography.

To ensure physiological night ventilation in severe OSAS patients, nasal continuous positive airway pressure (N-CPAP) is initiated before LAUP, as an adjunct to the surgical intervention. Polysomnography is carried out before and after surgery. After LAUP, sleep efficiency (total sleep time x 100 / total sleep period) measured by nocturnal EEG is often improved, with longer periods

spent in stage III-IV and REM sleep. CPAP can be discontinued when the polysomnography results become close to normal.

Most of the usual symptoms of OSAS are improved after LAUP: snoring, daytime sleepiness, morning tiredness, morning headaches, frequent awakening during sleep, and sexual problems (erection dysfunction, loss of libido). Some patients notice a reappearance of dreaming. A complete cure or clear improvement of OSAS was usually achieved in patients with mild or moderate symptoms, with at least a 50% reduction in both the preoperative oxygen desaturation index and the preoperative sleep apnea index. Moreover, there is often a reduction in the duration of the apneas. Even if severe OSAS is not a good indication for LAUP, patients treated may have better long-term acceptance of CPAP, because of the reduction in the upper respiratory tract obstruction.

In the case of UPPP, a high respiratory disturbance index (RDI) and sleep apnea index, and morbid obesity also predicted a poor response to LAUP.

Most patients feel better after LAUP treatment. Daytime somnolence is a significant subjective problem. It is present in 3-12% of the population. Twenty percent of people older than 64 years complain of this symptom. The treatment of daytime somnolence can be very helpful in the prevention of traffic accidents. Some patients admit to driving poorly or to reacting slowly because of daytime somnolence. Driving efficiency is correlated with the subjective assessment of vigilance. After the treatment of snoring, there is improvement in daytime somnolence and in the patients' driving skills.

## Conclusions

LAUP can lift drooping soft palates on both sides of the uvula, similar to the way in which a theater curtain rises. It has many advantages over a scalpel or radiofrequency in surgery for snoring. Unlike the scalpel, the laser can coagulate, vaporize, and cut the velum, the posterior pillars, and the uvula. It also decreases postoperative edema and pain, and allows quicker and better cicatrization. Because of the hemostatic action of the laser, the procedure can be performed under local anesthesia, with minimal bleeding from the highly vascular tissue of the oral mucosa.

LAUP is better tolerated than conventional UPPP, allowing the patient to return to work immediately following the procedure. There is less tissue swelling, resulting in less pain and scar tissue, and in better healing than the traditional surgical procedure. Bleeding is minimal because of the cauterizing effect of the laser.

LAUP allows more precise cutting, less tissue loss, and better overall control. It is more attractive to surgeons who question traditional UPPP, because of its anesthetic risk and increased postoperative pain. Limited palatal resection ensures success of the operation and the avoidance of nasal regurgitation of food or rhinolalia postoperatively.

LAUP may also be a good alternative for patients who present with major surgical- and anesthesia-related risks. In all cases, the healing of laser-induced wounds is faster than after the usual UPPP, except in the case of alcohol or tobacco use. In these cases, the duration of postoperative pain is prolonged.

After 12 years of clinical experience with LAUP, in our hands, this technique has improved or eliminated snoring and OSAS in most cases. It is now routinely used in non-apneic snorers, and in mild and moderate OSAS, as these results have been confirmed by other investigators. In our common practice, it is often very important to associate nasal and tonsil outpatient laser surgery, when the nose and pharyngeal or lingual tonsils are the secondary site of airway obstruction.

Compared to radiofrequency tissue volume reduction, the immediate success rate of LAUP is even higher, with better long-term results, and similar postoperative discomfort, if the Ketoprofen pain-killer injection is used.

When performed in properly selected patients, LAUP is an effective, simple, safe procedure, well tolerated by snorers. It has become a valuable technique to replace the now conventional UPPP, with its great potential for reducing morbidity and the costs to the patient. The popularization of LAUP necessitates serious training of surgeons and further study, especially in OSAS surgery, which is more difficult to treat, because of the thickness of the soft palate. In these patients, long-term polysomnographic controls are necessary in order to study the long-term results.

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# LASER-ASSISTED UVULOPALATOPHARYNGOPLASTY

## A meta-analysis

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### Introduction

Since 1981, uvulopalatopharyngoplasty (UPPP) has gained acceptance as a routine therapy in the surgical treatment of sleep-related breathing disorders (SRBD).[1] As an essential modification of conventional UPPP, laser-assisted velum surgery was developed, which was introduced by Carenfelt in 1986,[2] and which he called laser uvulopalatoplasty (LUPP). While Carenfelt performed LUPP under general anesthesia and with sutures similar to those used with UPPP, at the end of the 1980s, Kamami[3-5] introduced a further modification which was carried out under local anesthesia during several sessions on an outpatient basis. This modification was called laser-assisted uvulopalatoplasty (LAUP) and rapidly took hold in Europe and also became increasingly popular in the USA after 1992.[6]

Up to March 2000, more than 70 articles on LAUP had been published worldwide. However, the clinical relevance was not always clear. Therefore, this presentation will attempt to structure the literature on the basis of clinical criteria, in order to highlight the significance of LAUP/LUPP in everyday routine work. In particular, indications for LAUP/LUPP, their prospects for surgical success, and the complications encountered, will be clarified.

### Surgical techniques

Twenty-four publications describe the surgical techniques in detail, explaining which of the anatomical structures in the soft palate are involved. Most of these publications are illustrated with explanatory drawings or photographs. Although the variability of the techniques described is very high, three basic techniques can be identified.

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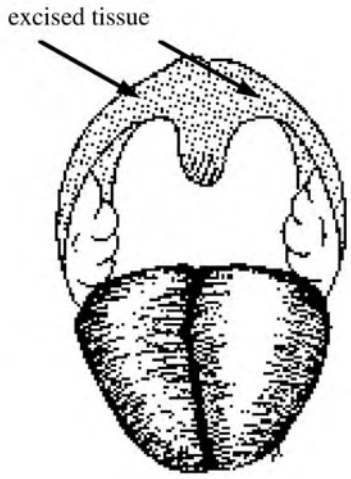


*Fig. 1.* Scheme for LUPP. (Reproduced from Wennmo et al.[7] by courtesy of the *Acta Otolaryngologica*.)

The oldest technique, proposed by Carenfelt in 1986,[2] is LUPP, which was reported by two working groups to be more gentle to the muscles,[2,7,8] and by three other working groups to be substantially more radical.[9-12] The LUPP procedure is similar to UPPP, *i.e.*, it also extends to the pharyngeal walls and partly to the tonsils (Fig. 1). The Carenfelt and Haraldsson working group used suture techniques for adaptation of the posterior to the anterior column of fauces, in order to prevent uncontrolled scarring.

Most authors apply the LAUP technique introduced by Kamami,[3] during which para-uvular vertical incisions are made throughout the soft palate. The uvula is partly or totally removed. With one exception,[13] LAUP is performed under local anesthesia in an outpatient setting. There is also a more radical one-stage technique (Fig. 2) and a more gentle procedure performed during several (up to five) sessions (Fig. 3).

The most recent modification is described in detail by two working groups.[14,15] This technique differs from the others by only removing the mucosa and not the velum musculature in the area of the anterior palatine arch (*M. palatoglossus*). The uvula and the posterior tonsillar pillar are treated in the same way as during LAUP and LUPP (Fig. 4). Morar *et al.* call this modification the mucosal strip technique (MST).[14]

In most cases, the $CO_2$ laser is used. No comparisons regarding differences between the various types of lasers have yet been found in the literature. However, in an animal test performed on six dogs, Ducic *et al.*[16] were able to show that the $CO_2$ laser caused deeper thermal tissue damage and more intensive scarring than the conventional UPPP technique using bipolar coagulation.

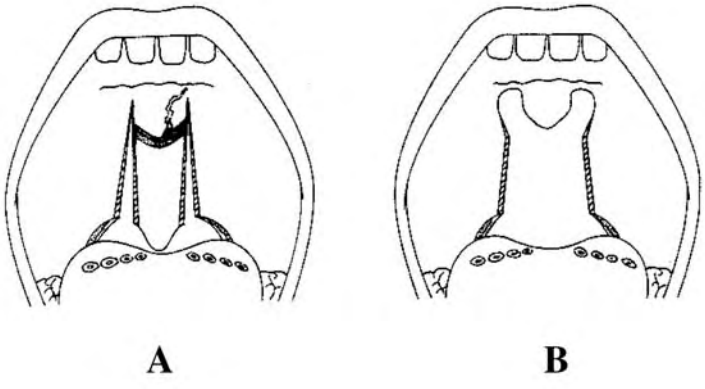


*Fig. 2.* Scheme for one-stage LAUP. (Reproduced from Kamami[40] by courtesy of the publisher.)

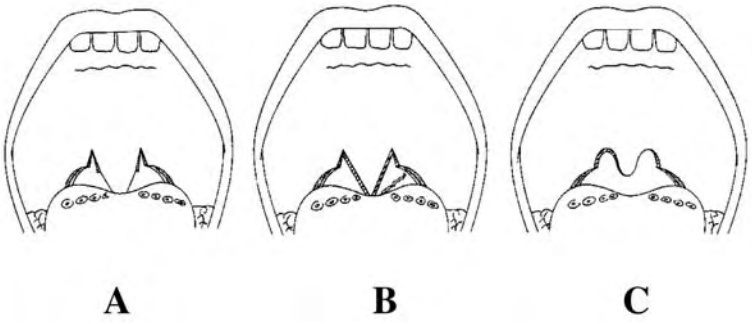


*Fig. 3.* Scheme for LAUP in multiple stages. (Reproduced from Kamami[40] by courtesy of the publisher.)

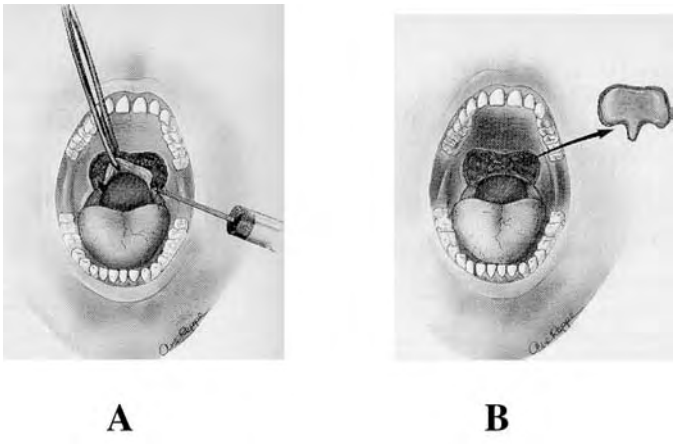


*Fig. 4.* Scheme for MST with resection of the uvula. (Reproduced from Skatvedt[15] by courtesy of the *ORL Journal of Otolaringology and Related Specialties*.)

**LAUP and obstructive sleep apnea**

Only eight studies,[17-24] covering a total of 232 patients (Table 1), provided pre- and postoperative information on the apnea-hypopnea index (AHI) and/or the apnea index (AI). No other studies were taken into consideration, since they did not provide enough information.

In his earlier study, Mickelson reported on 13 patients with obstructive sleep apnea (OSA).[25] Since the investigation period is identical in both studies, only the more recent study covering 33 patients was considered,[23] in order to prevent patients from being included twice in the evaluation. The same applies to the earlier studies of Walker *et al.*[26,27]

Comparison of the eight studies mentioned above has been made difficult by the fact that different definitions of OSA and different success criteria were used. This problem has already been mentioned by the American Sleep Disorders Association[28] and by Hoffstein.[29] The value given for the lower limit when assessing the presence of OSA varies between not mentioned,[17] AI > 5[18] and AHI > 5[19,21,24] to AHI > 10.[20,23] Success criteria for LAUP were not mentioned by two authors.[19,20] One author requested at least a 50% reduction of respiratory events.[17] Petri *et al.*[18] define a reduction of AI to below 50% or to values below 20 as a success criterion. This working group mentions a cure as having an AI reduction to values below 5. In contrast, only Utley *et al.*[21] agree with the criteria recommended by Sher *et al.*[30] for UPPP: AHI reduction to below 50% and AHI reduction to values below 20, or AI reduction by at least 50% and to values below 10. Walker *et al.*[24] use several definitions, as do Mickelson and Ahuja.[23]

It is remarkable that no long-term results have yet been published. While Terris *et al.*[19] present results obtained after two to three days, the other authors report on findings obtained between two and five months after surgery. Ages vary between 40.8[19] and 56 years,[21] the body-mass index between 28[18] and 31.0 $kg/m^{-2}$.[23]

The AHI is presented for 202 patients, and decreases from a presurgical value of 29.1 to a value of 23.4 after surgery. However, four working groups[19-22] reported an increase in the AHI postoperatively. The same trend can be observed for the AI in 203 patients (Table 1).

A comparison of the success rate of surgery is not possible due to the different criteria applied. Figures vary between 24.1%[22] and 87.3%.[17] *Cum grano salis*, all the results obtained in 208 patients yield an overall success rate of between 52.9 and 67.4%. Without taking into consideration the most extreme values,[17,22] the cumulative success rate (calculated in 116 patients) is between 48.4 and 65.4%. These values are above those calculated by Sher *et al.*[30] in their meta-analysis (40.7% in 345 patients) of UPPP. The average postsurgical observation period was 3.2 months.

Terris and Wang[31] also studied the literature on LAUP and OSA in 1998. Based on articles published up to that time, their analysis yielded an average

*Table 1.* Original papers on LAUP/LUPP for the treatment of OSA

| *Author* | *n (232)* | *Age (years)* | *BMI (kg m$^{-2}$)* | *Follow-up (months)* | *AHI pre-* | *AHI post-* | *AI pre-* | *AI post-* | *Success rate (%)* | *Sessions* |
|---|---|---|---|---|---|---|---|---|---|---|
| Kamami 1994[17] | 63 | 52.8 | 29.4 | no data | 41.3 | 20.3 | 28.4 | 7.7 | 87.3 | 3.8 |
| Petri *et al.* 1994[18] | 30 | 47 | 28 | 5 | no data | no data | 26.0 | 7.0 | 47–73 | 1 (LUPP) |
| Terris *et al.* 1996[19] | 7 | 40.8 | no data | 2–3 days | 11.3 | 21.7 | 3.3 | 14.8 | no data | 1 |
| Lauretano *et al.* 1997[20] | 17 | 50 | 28.6 | 2 | 27.9 | 29.1 | 7.6 | 7.9 | no data | 2.6 |
| Utley *et al.* 1997[21] | 12 | 56 | no data | 4 | 8.9 | 10.3 | 2.0 | 2.3 | 41.7 | 2.4 (+TE) |
| Mickelson and Ahuja 1999[23] | 36 | 52.3 | 31 | 4 | 28.1 | 17.9 | 14.4 | 5.8 | 33.3-66.6 | 2.7 |
| Pribitkin *et al.* 1999[22] | 29 | 53.5 | 30.2 | 1-3 | 15.8 | 41.3 | no data | no data | 24.1-32 | 1.9 |
| Walker *et al.* 1999[26] | 38 | 53.6 | 29.5 | 3 | 30.3 | 22.2 | 20.1 | 14.6 | 44.8-65.8 | 4 |
| Mean | | 51.8 | 29.5 | 3.2 | 29.1 | 23.4 | 19.8 | 8.5 | 52.9-67.4 | |

BMI: body-mass index; AHI: apnea-hypopnea index; AI: apnea index

success rate of 66.5% in 191 patients. This value is at the upper limit of the success rate obtained in the present meta-analysis. One explanation for this is that, on the one hand, two working groups[23,24] re-evaluated their data after defining stricter success criteria, and the inclusion of a more recent, but less successful series[22] on the other.

Tsushima *et al.*[32] reported on a series of 33 patients with OSA who underwent LAUP, who had been examined by lateral digital fluoroscopy, a static-charge-sensitive bed (SCSB) with body position sensor and pulseoximeter. Based on the results of the measurements, the patients were allocated to four categories of severity (simple snorers, and patients with mild, severe, and total obstruction). Postoperative allocation to a lower category was rated as a success. Six months postoperatively the success rate was 70.8%, and a deterioration of their situation was observed in three patients (9.1%). In particular, patients who were seriously ill presurgically did not benefit from LAUP. Although this study cannot be compared with the others, due to the lack of polysomnographic data, the results confirm the overall trend.

To assess the effectiveness of soft palate surgery for OSA, the same success criteria have to be used. In this way, Mickelson and Ahuja[23] only showed a variation in the success rate of surgery of between 33 and 67% in the same patients by applying different criteria. Comparable results were published by Walker *et al.*[24] and Lauretano *et al.*[20]

## Complications

In a survey of complications occurring in Sweden after soft palate surgery for SRBD,[33] three deaths were reported in 9000 UPPPs and one death in 2900 LAUPs. The latter patient died of sepsis on the fourth postoperative day, since perioperative prophylaxis with antibiotics had not been carried out.

Generally, all kinds of soft palate surgery, and in particular radical procedures, carry the danger of the limited acceptance of later nasal continuous positive airway pressure (CPAP) therapy, due to the occurrence of oro-nasal airflow leakage.[34] Moreover, in 25 studies, further complications after LAUP are mentioned. These are summarized in Table 2, together with the frequency whenever this was stated. The postsurgical observation period ranged from 48 hours[19] to eight years.[35]

Long-term complications are particularly exhausting for the patients. There are almost no data to be found regarding this problem. Petri *et al.*[18] described permanent reflux in the nasopharynx in three of their 30 patients, and Grontved *et al.*[36] reported this in one of 21 patients. Pinczower[37] described a foreign body sensation six months after surgery in two of 60 patients. This author deals with this problem in more detail in his study. He was able to prove that parauvular incisions caused damage to the sensitive innervation of the neo-uvular area, which is medial to the incisions. This in turn causes a foreign-body sen-

*Table 2.* Complications after laser-assisted surgery on the soft palate, according to frequency

| *Complication* | *Incidence (%)* |
|---|---|
| Nasal regurgitation (short-term) | 80 |
| Sore throat | 46 |
| Scar fibrosis | 27 |
| Velopharyngeal incompetence | 1.5-26.7 |
| Dysphagia | 6-26.6 |
| Foreign body sensation | 9-25 |
| Paraesthesia | 22 |
| Aspiration | 21.5 |
| Occurrence of other disturbing breathing sounds | 20.5 |
| Voice problems | 1.3-20 |
| Irritation of taste | 0.7-18 |
| Xerostomia | 16 |
| Wound infection | 1.5-14 |
| Odynophagia | 1.4-12 |
| Vomiting | 10 |
| Nasal regurgitation (long-term) | 4.8-10 |
| Postoperative bleeding | 0.7-10 |
| Hypersalivation | 5 |
| Nasopharyngeal stenosis | 0.1-3.3 |

sation, which may sometimes lead to vomiting,[13] but which apparently abates in most cases. Nasopharyngeal stenosis was reported in 0.1-3.3% of all cases, and must be seen as a permanent complication.

Comparison with UPPP is particularly valuable for the assessment of complications occurring with LAUP, when the same surgeon uses both surgical techniques, and such a comparison can be found in five publications. Carenfelt[2] described a significantly higher rate ($p > 0.05$) of scarred nasopharyngeal stenosis after LUPP compared with after UPPP. Chabolle *et al.*[38] found less velopharyngeal incompetence after LAUP (5% versus 10%) and less dysphagia (15% versus 23%), but more pharyngeal paresthesia (22% versus 18%), wound infections (10% versus 5%), and general painfulness (44% versus 41%).

In contrast, in a radiocephalometric examination with a contrast agent, Finkelstein *et al.*[12] proved obstruction of the nasopharynx with LAUP and dilation of the nasopharynx with UPPP. In an investigation carried out by Shehab and Robin[39] the patients reported significantly more pain ($p = 0.0027$) after LAUP than after UPPP on the seventh day post-surgery. No significant difference was found on the first postoperative day. In a collective consisting of 110 patients with OSA and 254 simple snorers, Hagert *et al.*[35] reported the postoperative occurrence of other disturbing noises during sleep. These noises (smacking, grunting, whistling) were observed in 20.5% after LUPP, but in only 15.1% after UPPP.

## Indications and contraindications

Indications and contraindications will be discussed separately for surgical procedures, associated illnesses, local findings in the upper airway, and severity of SRBD.

In total, 19 working groups comment on LAUP in this connection. The following associated illnesses are mentioned as contraindications: overweight,[37,38,40,41] arterial hypertension,[6,42,43] and mental irregularities or lacking cooperation.[6,42,43] Being a professional speaker or singer was also seen as relative contraindication.[42,43] In cases in which another kind of surgery was also indicated, Utley *et al.*[21] recommended UPPP under general anesthesia, rather than LAUP. The following illnesses are named as local factors: tonsillar hypertrophy,[37,44] trismus,[6,42,43] craniofacial malformation and cleft palate,[6,42,43] macroglossia,[48] prominent plication of the rear oropharynx wall,[26,27,45,46] heavy retching,[26,27,45,46] previously existing velopharyngeal incompetence,[42,43] floppy epiglottis,[40] and neuromuscular diseases of the pharynx.[6] A retrolingual site of collapse alone is also seen as contraindication.[23,25-27,40,42,43,45,46]

Contradictory statements have been made regarding the severity of SRBD that also require laser-assisted surgery. Finkelstein *et al.*[12] express the most restricted opinion, since they do not consider LAUP to be indicated for both simple snoring and OSA. In a direct comment, Terris[47] disagrees with this view. Sixteen of 19 working groups think that there is an indication for LAUP in simple snoring, ten of 19 in mild OSA, five of 19 in moderate OSA, and one of the 19 working groups would consider LAUP for the treatment of severe OSA. Two further working groups also indicate LAUP to be an alternative treatment in severe OSA when nasal CPAP therapy has failed.[23-27,45,46] It is remarkable that, in their first four publications,[26,27,45,46] the Walker working group found that an AHI of 20 was the upper limit for an indication for LAUP, while in their most recent publication,[24] they felt that LAUP was indicated in all categories of severity of OSA.

Only six studies deal with the upper airway resistance syndrome (UARS).[48] Five of these six groups performed LAUP in patients with UARS.

To date, LUPP has only been recommended for the treatment of simple snoring.[2,7] Tonsillar hypertrophy as a local factor and all categories of OSA severity are put forward as contraindications.[6]

MST is also used in the treatment of simple snoring.[14,15] Skatvedt[15] also sees an indication for this in OSA, if the site of obstruction has been proved to be in the velopharynx, while Morar *et al.*[14] consider OSA to be a contraindication for this surgical procedure.

## Predictive criteria

Fifteen working groups have searched for criteria to predict operative success. They suggest the following criteria: lower BMI,[18,26,36,38,41,49] lower severity of

OSA,[18,22,26,32,42,43,49] site of obstruction in the velopharynx,[23,47,48] female gender,[22,24] velopharyngeal obstruction pattern,[12,51] lack of loud snoring and apnea,[52] exclusion of craniofacial malformations,[18] and lower age.[22,24] A clear trend cannot be recognized, which can mainly be explained by the fact that the definitions for success are too diverse.

## Discussion

In 1994, the American Sleep Disorders Association (ASDA) issued a declaration containing five statements regarding laser-assisted surgery of the soft palate, as follows:[28]

1. Use in the treatment of SRBD was generally rejected due to the lack of adequate peer-reviewed objective data.
2. Surgical candidates for LAUP require preoperative objective measurement of respiratory parameters during sleep (polysomnography).
3. Patients must be informed that the risks, benefits, and complications of LAUP have not yet been established.
4. Patients who undergo LAUP/LUPP for the treatment of simple snoring must be informed that OSA may be masked by the successful surgical treatment of snoring, and therefore, this may delay the diagnosis of OSA.
5. The perioperative use of narcotics is connected with a risk in patients who are being treated with LAUP/LUPP.

Up until March 2000, ASDA has not issued any other comment. However, in the meantime, numerous articles have been published on this topic, so that, from the present point of view, the following comments can be made on the five statements mentioned above:

Statement Nos. 2, 4, and 5 are still true. In this connection, no other or different knowledge is expected to be gained. The majority of authors now considers that pre- and postoperative polysomnographic sleep studies are vital in the assessment of the operative results of soft palate surgery for the treatment of OSA.

However, the use of LAUP and its related procedures cannot generally be rejected based on our present knowledge (statement No. 1). With regard to the therapy of simple (primary) snoring, long-term data are available for observation periods of up to 60 months.[6,38] Prospective examinations show success rates of 61.4-83.4%, depending on the surgical procedure applied. With regard to the treatment of OSA, data from prospective examinations are available in a total of 232 patients. However, the maximum postoperative observation period is five months (Table 1).[18] Further objective prospective long-term data are still required. The short-term results are promising and are slightly higher than the success rates for conventional UPPP.[30] The use of LAUP and its related

procedures cannot yet be generally recommended for OSA therapy. Accordingly, in a more recent survey dated 1999, Barthel and Strome[53] only consider mild OSA and simple snoring as indications.

Statement No. 3 is largely invalid in the light of today's knowledge. We usually know how things stand regarding the risks and complications connected with LAUP and its related procedures (Table 2). As already stated, the benefits of the above-mentioned procedures cannot be definitively assessed, since long-term results regarding OSA are still lacking.

Further prospective long-term studies are required. However, it will only be possible to evaluate these studies if standard measuring instruments for the assessment of breathing sounds, as well as standard criteria for the assessment of surgical success, are established. According to the various authors, visual analogue scales for snoring and the success criteria recommended by Sher *et al.*,[30] *i.e.*, AHI reduction by at least 50% and to values below 20, have proved to be effective.

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# INTERSTITIAL DIODE LASER TREATMENT FOR OBSTRUCTIVE SLEEP APNEA SYNDROME

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In our experience, within the present scope of possible therapies for carefully selected snoring patients, the interstitial laser represents the least traumatic, least painful, and therefore most approved, manner of treatment. The idea of the treatment is to obtain the effect of thermotherapy that the interstitial diode laser induces in hematic tissues such as the highly vasularized nasal and soft palate linings.

Conversion of the laser radiation energy into heat allows specific photocoagulation of the vascular deep tissues, keeping damage to a minimum compared to non-vascular tissues. This phenomenon known as scattering has to do with the affinity of the laser ray to hemoglobin pigment, and it determines the intratissue photocoagulative effect of the surrounding zones, allowing, after the treatment, progressive and ultimate retraction of the tissues. It resolves continuing destruction of the vascular layers in the path of the diode laser fiber, without changes to other anatomical structures.

The thermotherapy system used by us consists of:
- a diode laser (805 nm)
- a fiber 600 μm in diameter

We use a power of 0.5-25 W for one-minute applications. We treated 25 patients (19 males, six females), aged between 21 and 45 years, under local anesthetic. In all cases, complete medical history was obtained and the classic presurgical examinations performed. Any patients affected by obstructive sleep apnea syndrome (OSAS) with a respiratory disturbance index (RDI) of >15 were excluded, as were those suffering from pathological nasal stenosis and patients already operated on by other techniques, with unsatisfactory results. All the patients gave written consent and were informed of the expected results, side-effects, and any possible complications.

The interstitial laser treatment was carried out on an outpatient basis, under local anesthetic. The points where the fibers are attached are on the soft palate.

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Three points are emphasized that are: *(a)* 1 cm above the base of the throat; *(b)* in the area equidistant between the throat and the front of the soft palate, in correspondence with the margins behind the raised muscle of the palate. A power of 10 W is introduced into the fiber. The photocoagulation effect is produced with 4 W and lasts for 60 seconds. A hypochromia is visible around the interstitialized area. A retraction of about 5-8 mm is immediately obtained. Follow-up was performed after one week, and one, three and six months.

In our experience, the success rate of interstitial laser treatment was 76%. We believe that the interstitial technique using a diode laser in suitably selected patients, is a valid alternative to classical laser-assisted uvuloplasty (LAUP). It has the advantages of lack of anatomical alteration, minor invasiveness, reduction of pain, and the attainment of results substantially comparable to LAUP. It is our opinion that not modifying the anatomical parameters of the palatal region and, therefore, of retaining the possibility to be able to use oxygen therapy with continuous positive airway pressure (CPAP), and also extending the technique to patients with silent or medium OSAS, is helpful for improving the problem of snoring.

# RADIOFREQUENCY ABLATION OF THE SOFT PALATE (SOMNOPLASTY®) IN THE TREATMENT OF HABITUAL SNORING

## Results of a European multicenter trial

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### Introduction

Snoring is a considerable problem in a large number of people. Besides being a social nuisance, there is increasing evidence that snoring (without obstructive sleep apnea) may be harmful and may contribute to excessive daytime sleepiness, cardiovascular disease, and arterial hypertension.[1] Uvulopalatopharyngoplasty (UPPP) is the most common surgical procedure for simple snoring, with the successful relief of snoring in 75-100% of subjects on a short-term basis.[2] Side-effects are frequent in the immediate postoperative period and long-term sequels may occur.

Radiofrequency thermal ablation of the soft palate (Somnoplasty®), is a surgical method that uses radiofrequency heating to create temperature-controlled, targeted tissue ablation, resulting in tissue volume reduction of the soft palate.[3] A prospective, non-randomized, multicenter European study was set up to investigate the effect of Somnoplasty® on snoring, and to determine a safe and effective treatment protocol.

### Material and methods

Patients with a respiratory disturbance index (RDI) <15 events/hour, as documented by full night polysomnography and body mass index <30 kg/m$^2$, seeking treatment for socially disturbing snoring, were considered eligible to participate in this study. Each patient underwent one to a maximum of three treatment

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sessions, depending on the improvement in snoring obtained, and separated by an interval of four to six weeks.

A full night polysomnography was performed before the first, and eight weeks after the last, treatment session. Also, patients who were not satisfied with the improvement in snoring after three sessions underwent a final evaluation eight weeks after the third session. Subjective snoring was assessed by a visual analog scale (VAS) ranging from zero (no snoring) to 10 (very intense snoring causing the bedpartner to leave the room), resulting in a snoring index. A VAS was used to investigate post-treatment pain and other side-effects. These questionnaires were completed before the first procedure, eight weeks after the last procedure, and at each interim visit. An Epworth sleepiness scale was completed before the start of the study and at the final evaluation.

Somnoplasty® was performed on an outpatient basis under local anesthesia. A radiofrequency generator with custom-fabricated needle electrodes and delivery device was used (Somnus Medical Technologies Inc. Somnoplasty™ System, Sunnyvale, CA). The needle was inserted in the midline of the soft palate and a total amount of energy of ~700 J was delivered at each session.

## Results

A total of 45 subjects, 38 males and six women (one unknown gender) was included in this study. The patients were non-obese (BMI 26.6 (3.2) kg/m$^2$), middle-aged 43.7 (10.9) nonapneic snorers, respiratory disturbance index (RDI) 5.1 (4.3) events/hour. Two patients underwent one treatment session, nine subjects had two sessions, and the remaining 34 subjects were treated three times. The total amount of radiofrequency energy delivered/session was 692.3 (67.7) J.

For the group as a whole, Somnoplasty® resulted in an improvement in subjective snoring (snoring score), the mean difference was 3.6 (2.7) $p < 0.001$. Twenty patients (44%) were treated successfully (snoring score of 3 or less) and, in 38 patients (84.4%), snoring improved. Improvement in daytime sleepiness was also observed. The Epworth sleepiness scale decreased from 8.5 (5.0) to 6.0 (4.3), $p = 0.001$. No change in RDI was documented.

The patients experienced little pain, as illustrated by the VAS score: 1.0 (1.4) on postoperative days 1-3; 0.4 (1.0) at weeks 1-2; and 0.1 (0.5) at week 4. There were no major adverse events. The most frequently encountered side-effect was mucosal erosion ($n$=19). Other side-effects were excessive swelling ($n$=1), fistulization ($n$=1), uvula loss ($n$=1), and hemorrhage ($n$=2).

## Discussion

Our results demonstrate that the current protocol (one midline lesion/session, maximum three sessions) has a modest effect on subjective snoring in indi-

vidual patients. Forty-four percent of the patients could be considered to have been successfully treated, while 84% experienced improvement in snoring. In the remaining patients, no improvement or worsening of snoring was observed. Although the patients were not abnormally sleepy at baseline, an improvement in the Epworth sleepiness score was documented. Somnoplasty® is a safe procedure causing minimal pain/discomfort and has no major adverse events.

The protocol recommended ablation of the soft palate at or near the midline, with an accumulated energy per session in the range of 500-750 J. In addition, each patient was offered a maximum of three sessions. It would appear to be worthwhile to investigate whether the outcome would be improved by using additional lesion sites (for example, paramedian or lateral to the soft palate), delivering more energy or increasing the number of treatment sessions. In the present study, anatomical features of the pharynx, such as hypertrophied tonsils or excessive mucosal folding, were not considered a selection criterion. Because Somnoplasty® is only applied to the uvula and soft palate, we speculate that it would be most successful in patients without other structural pharyngeal abnormalities.

## Conclusions

Radiofrequency thermal ablation applied solely at the midline of the soft palate, with an energy of ~700 J/session and a maximum of three sessions, improves snoring in the majority of patients. Because this treatment can be used in an outpatient setting, under local anesthesia, is associated with minimal pain or discomfort, and results in thermally controlled radiofrequency treatment, we recognize that it may have substantial advantages over other forms of treatment for snoring, such as UPPP. We therefore suggest that other treatment schedules be explored in order to improve the outcome of this new treatment for simple snoring and mild obstructive sleep apnea. In addition, further studies are necessary to investigate whether particular anatomical features (such as tonsillar hypertrophy) affect the outcome of Somnoplasty®.

## Acknowledgement

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# UVULOPALATOPLASTY FOR SNORING AND MILD OBSTRUCTIVE SLEEP APNEA

## Experience in 280 patients

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### Abstract

The authors report on a series of 280 patients with simple snoring and mild obstructive sleep apnea (OSA), who were treated in an outpatient setting, and who were selected after an initial questionnaire and other usual preoperative evaluations. Polysomnographic (PSG) evaluation was carried out if required (high or moderate chance of OSA). The same surgical procedure was used with different devices: $CO_2$ laser (LAUP); diode laser (DAUP); radiofrequency (RFUP). Complications were extremely rare with any of the three methods, and pain was the major side-effect. Complete or nearly complete elimination of snoring was obtained in almost 70% of the patients.

### Introduction

Between February 1996 and May 1997, 280 patients with snoring problems were evaluated for uvulopalatoplasty (UP) in an outpatient setting at the ENT Department of Valle Camonica Hospital, Esine (BS), Italy.

### Material and methods

The patients and their partners answered a detailed sleep questionnaire, which was followed by a thorough ENT examination. If the chance of obstructive sleep apnea (OSA) was low after review of the questionnaire and the ENT examination, the patient underwent UP in an outpatient setting; if the chance of OSA was moderate or high, the patient underwent polysomnographic (PSG) screening; and if the respiratory disturbance index (RDI) was more than 40, the patient underwent further examinations with other specialists, such as,

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pulmonologists or dietitians, and complete PSG. However, surgery was not the first choice of procedure, rather this was continuous positive airway pressure (CPAP) and mechanical ventilation. If CPAP failed or was refused by the patient, other investigations, such as, MRI or cephalometric X-ray, were carried out in order to decide which major surgical technique should be implemented (mandibular repositioning, tongue base surgery, tracheotomy, etc.). If PSG screening showed that the RDI was less than 40, the patient underwent UP in an outpatient setting. Contraindications to an outpatient procedure are: severe sleep apnea, uncontrolled hypertension, cleft palate, velopharyngeal insufficiency, severe trismus, serious obesity, an uncooperative patient, bleeding disorders, and mandibular retromicrognathia.

*Surgical technique*

A vertical transpalatal incision, approximately 1 cm in length, is made near the uvula, as well as a partial cut of the uvula. One or more treatments with other minimal procedures, such as turbinotomy or tonsillotomy, are carried out if required.

*Complications*

Complications were very rare with any of the three methods used ($CO_2$ laser UP (LAUP); diode laser UP (DAUP); radiofrequency UP (RFUP)).

## Results

Our criteria for success consisted of questionnaires and telephone calls to the patients; moreover, a new PSG was performed to evaluate the reduction of the RDI if this had been more than 20 preoperatively. Complete or nearly complete elimination of snoring was seen in almost 70% of the 280 patients (LAUP: 170 patients; DAUP: 25 patients; RFUP: 85 patients).

## Discussion

In our experience, it is critical to identify the level of collapse during sleep. Moreover, body weight plays an important role.

With regard to follow-up, most of our patients lived some distance from the hospital, and only 12 underwent a new PSG at the end of treatment. Therefore, the results of this first study of pre- and postoperative RDI are not statistically significant. In other words, we do not yet have a preoperative method for selecting responders and non-responders to UP in an outpatient setting. For this reason, careful selection of the patient is the most important consideration for the success of this surgical procedure.

## Conclusions

It is our opinion that, under local anesthetic and in an outpatient setting, LAUP, DAUP and RFUP are comparable in terms of results and complications.

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# UVULOPALATOPLASTY BY RADIOSURGERY

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## Introduction

Recent surgical procedures on the palate in subjects with sleep-disordered breathing include a new treatment: surgery by radiofrequency (RF).[1,2] There are two ways of using RF: radio-assisted uvulopalatoplasty (RAUP) and submucosal radio-assisted uvulopalatoplasty (SRUP) or radiofrequency ablation (RFA).

RAUP is similar to laser-assisted uvulopalatoplasty (LAUP): a special RF electrode is used to make a vertical through-and-through incision on both sides of the uvula and the uvula is then significantly shortened.[3]

In the case of SRUP or RFA, an RF needle electrode (10 mm active length with a 10-mm protective sheath) is placed inside the midportion of the soft palate and only the tissue adjacent to the unprotected portion of the needle will undergo ablation.

Radiofrequency in the treatment of the soft palate is used for snoring and mild obstructive sleep apnea syndrome (OSAS).

We present our experience regarding radiosurgery of the soft palate. Radiosurgery of the turbinates is also used in patients with nasal obstruction.[4,5] The presurgical evaluation includes fiberoptic nasopharyngoscopy used together with the Müller maneuver, polysomnography and, in some cases, cephalometric analysis.

## Material and methods

Nineteen patients were treated: 14 with upper airway resistance syndrome (UARS) and five with mild OSAS. All the patients were male with a mean age of 48 years (range, 28-66 years). Of the 19 patients, eight required general anesthesia for tonsillectomy or septoplasty at the same time. RAUP was performed in

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*Table 1.* Surgical procedures

| | |
|---|---|
| RAUP | 14 |
| SRUP | 1 |
| RAUP + SRUP | 4 |

RAUP: radio-assisted uvulopalatoplasty; SRUP: submucosal radio-assisted uvulopalatoplasty

*Table 2.* Surgical procedures performed in addition to RAUP and SRUP

| | |
|---|---|
| TRF | 14 |
| Tonsillectomy | 6 |
| MHS | 1 |
| Septoplasty | 2 |

TRF: turbinates radiofrequency; MHS: myotomy and hyoid suspension

14 patients, SRUP in one patient, and combined RAUP + SRUP in four patients (Table 1).

The combined RAUP + SRUP procedure is useful in the treatment of a very enlarged soft palate: the volumetric tissue reduction avoids an excessive excision and preserves the palatal incompetence.

In one patient, the hypopharyngeal airway obstruction was treated with myotomy and hyoid suspension (MHS) (Table 2).[6]

## Results

No immediate operative complications occurred. No important problems or palatal incompetence were observed postoperatively. Pain was acceptable and of short duration (0-48 hours). No infections were seen. Subjective snoring levels on the VAS score decreased from baseline by 76.5%. The reduction of sleepiness during the daytime was consistent.

## Conclusions

In our experience, radiosurgery is a minimally invasive procedure, which implies fewer complications. RAUP and SRUP are significantly less painful than any other snoring procedures and can be performed under local anesthesia in most cases. However, SRUP can be repeated when the result is poor.

In our opinion, the combination of RAUP and SRUP is probably the best procedure because the amount of tissue removed is small enough to avoid complications and, at the same time, the submucosal ablation reduces the thickness and increases the stiffness of the soft palate.

Further experience in a wide range of patients, as well as long-term results, will certainly be necessary to assess the effectiveness of these procedures.

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# COBLATION SURGERY FOR REDUCING TONSIL VOLUME IN SLIGHT OBSTRUCTIVE SLEEP APNEA SYNDROME

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## Abstract

*Objective:* Coblation (cold ablation) is a new technical weapon in soft tissue surgery. It is based on molecular dissociation and delivers very low calor to tissues transforming interstitial and cellular fluids into a 'plasma' scalpel. In benign tonsillar hypertrophy, it may be useful for reducing tonsillar volume in an office setting with a local anesthesia, rather than performing total tonsillectomy. *Study design and setting:* The authors studied the effect of Coblation surgery for tonsillar volume reduction (TVR) in a sample of 20 adults and ten teenagers affected by slight obstructive sleep apnea syndrome (OSAS; 15<RDI>30), in whom tonsillar hypertrophy was the major causal agent, by measuring the intertonsillar minimal distance (ITMD) before and after a six-month follow-up. OSAS was diagnosed and monitored by nocturnal polysomnography. *Results:* Mean initial ITMD was 6.14 mm; six months postoperatively, ITMD was 15.3 mm. RDI improved in all patients and became normal. *Conclusion:* Coblation TVR using local anesthesia may be able to avoid tonsillectomy in selected patients with slight OSAS due to benign tonsillar hypertrophy.

## Introduction

Tonsillectomy is a simple surgical inpatient procedure performed under general anesthesia. However, when using current methods such as electrocautery,[1] surgical scalpels or snares[2] or lasers,[3] risks and side-effects such as bleeding,[4] severe pain,[5] difficulty in swallowing, and increased snoring and apnea for at least two or three nights after the intervention, frequently occur.

When tonsil hypertrophy is not accompanied by a chronic infection, *i.e.*, when the patient has a normal blood index, a tonsil volume reduction (TVR) procedure under local anesthesia may avoid the complications linked to tonsillectomy. Since tonsil hypertrophy can cause obstructive sleep apnea syndrome

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(OSAS) or make it worse, and since these patients are often at risk for general anesthesia or present with anatomical difficulties regarding intubation (*e.g.*, short fat neck, huge tongue, etc.), TVR could be used to widen the upper airways, at the same time avoiding general anesthesia.

During the last few years, an interesting field of application for radiofrequency surgery has been the treatment of obstructive diseases causing snoring and sleep apnea.[6] Coblation®* (cold ablation) is a new technical weapon for use in soft tissue surgery. It is based on molecular dissociation and delivers very low calor to tissues transforming interstitial and cellular fluids into a 'plasma' scalpel. The limited amount of heat being delivered to the treated tissues is believed to be less damaging to the nerve endings. Coblation is a bipolar system and requires no connection to the patient. It replaces the thermally damaging vaporization and pyrolysis of standard electrosurgery with molecular disintegration via a cold ablative process. This is achieved by placing an electrically conductive fluid, such as isotonic saline, in the physical gap between the electrode and the tissue. Simultaneously with volumetric tissue removal by the shrinkage of collagen, the Coblation method is capable of producing coagulation of the smaller blood vessels located adjacent to the zone of ablation. This is effected by the residual current flow in the tissue, which extends beyond the plasma/tissue boundary.

## Methods

The clinical indications for TVR were based on how much the airway was obstructed, allowing patients to breathe better and, at the same time, reducing upper airway resistance and even snoring and sleep apnea.[7] ENT examination, cephalometry, endoscopy, and rhinomanometry were used to determine tonsil volume, in particular, as well as the precise site of the obstruction. Etiological diagnosis of tonsil hypertrophy was reached by clinical history and by excluding active tonsil or focal infection by means of hematic indexes (VES, ASLO, etc.) being within normal values. Diagnosis of slight OSAS was made using Simmond's scale on the basis of 15 <RDI (Respiratory Disturbance Index) >30 with nocturnal polysomnography (11 channels). Inter-tonsil distance (ITD) was assumed as an index of the quantity of volume reduction. It was measured in all patients prior to the intervention using a standard technique. The patient's head was placed on the chin rest of an ophthalmometer, a digital photograph was taken at a fixed distance with a Fuji 700 digital camera, and transferred to a PC. ITD (in mm) was measured digitally using commercial graphic software.

Coblation TVR was performed under local anesthesia on 20 adults (aged 21-47 years; mean age, 37.05 ± 6.99 years) and ten teenagers (aged 10-14 years; mean age, 12.9 ± 0.99 years) in an outpatient clinic. ITD of all these patients

*Coblation® is a process patented by Arthrocare Corpation.

ranged between 0 and 15 mm. Patients were treated with antibiotics for five days prior to the procedure.

A specialized surgical wand connected to the radiofrequency (RF) generator entered the enlarged tonsil at four locations equidistant from top to bottom of the tonsil body in a line at about 1 cm from the intraluminal tonsil border. RF energy was applied for 15 seconds at level 6 in a limited area around the electrode. Instrumentation was set to 'Coblation' action upon entering the tissue and to 'Coagulation' action when exiting the lesion. Diathermy was available and ready for use during the entire procedure. Antidolorific or corticosteroid therapy was available on demand during the days following. Any postoperative complications were recorded. All patients underwent a follow-up program, including nocturnal polysomnography and measurement of ITD at 15 days and at each month up to six months postoperatively.

Since the study was conducted during the winter period from October 1999 to May 2000, and since tonsil volume may have natural seasonal fluctuations, ITD was also measured in a group of controls not affected by OSAS (ascertained on polysomnography), homogenous for age and sex with ITDs ranging between 15 and 30 mm.

## Results

Patients did not experience any discomfort during the treatment. Three patients had slight pain on the following day. No patient had any hemorrhage or infection.

ITD measurements, performed at 15 days and at each month up to six months postoperatively, showed different shrinking behavior between the tonsils of adults and teenagers. Adults had a 'rebound' effect, *i.e.*, ITD decreased after 15 days, and then steadily increased up to the fourth postoperative month. In teenagers, the 'rebound' effect was minimal and ITD showed a steady proportional increase, which was still in progress at the sixth month. The non-operated controls showed minimal fluctuation of ITD (Fig. 1).

All patients, both adults and teenagers, were cured of their slight OSAS, since, after six months, RDI was within normal limits (>15). However, the recovery from OSAS was very different between the two groups, since, after 15 days, adults present ITD data that were totally uncorrelated with RDI ($r$ = -0.3441), while at six months, correlation was better but still far from complete, probably because tonsil hypertrophy could have been accompanied by occlusions at other sites, not evident clinically. In the group of teenagers, correlation was also very linear at 15 days ($r$ = -0.7426) and was still higher at six months ($r$ = -0.8724), showing that the airway occlusion was usually linked to tonsil hypertrophy (Fig. 2).

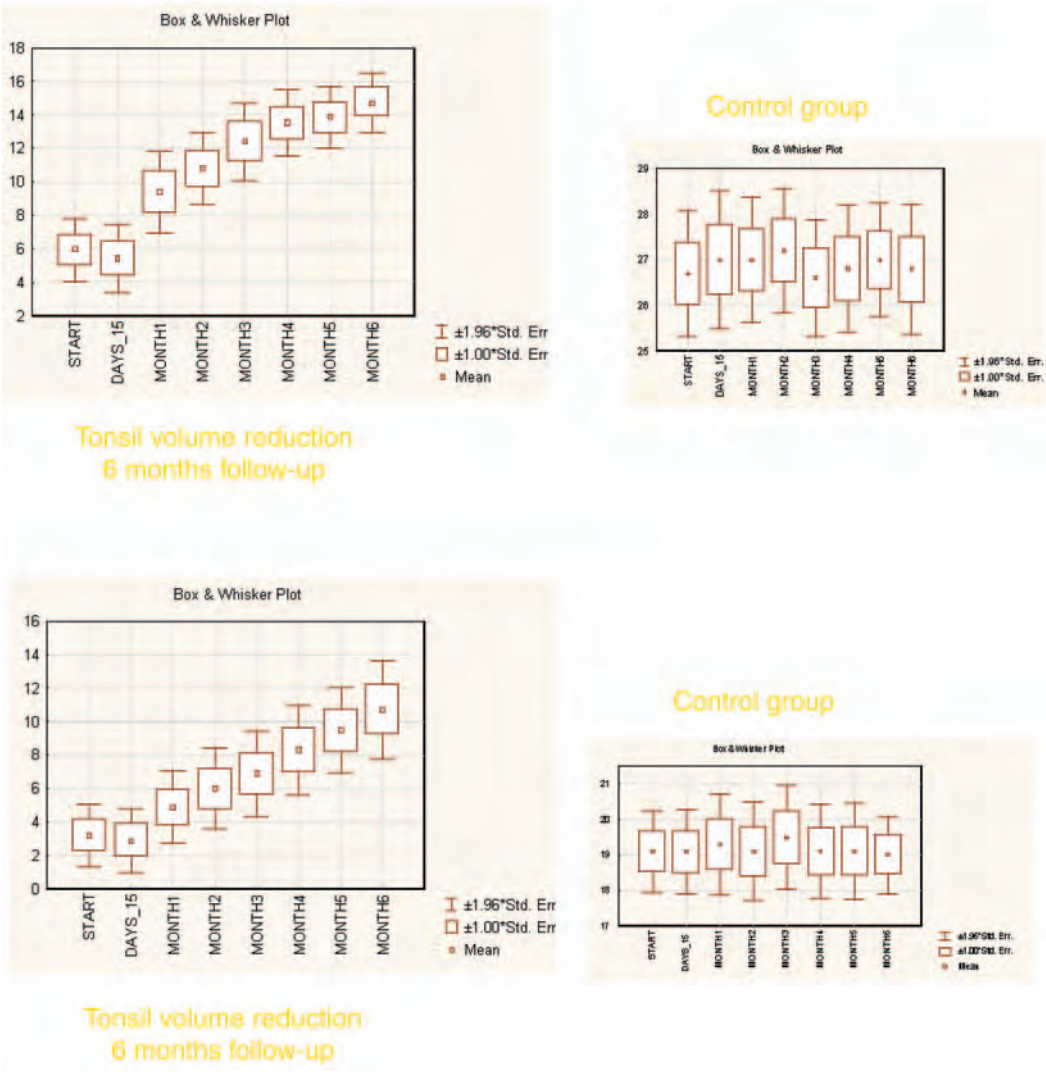


*Fig. 1. Left:* Mean values of ITD in 20 adults (top) and ten teenagers (bottom) versus length of time after TVR procedure (15 days and one to six months). Negative and positive 1.00 and 1.96 standard errors are also shown. In adults, ITD seems to decrease after 15 days, probably due to edema, and tends to stabilize at the fourth month. In teenagers, the increase in ITD seems more linear and lasts up to the sixth month. *Right:* Mean values of ITD in 20 adults (top) and ten teenagers (bottom) in the control group. Values were measured during the same months (October 1999-May 2000) as the study on the operated patients. Note that the ordinate scale is about one-quarter with respect to the graphics on the left. Therefore, fluctuations of ITD in normals with respect to seasonal events should be considered minimal.

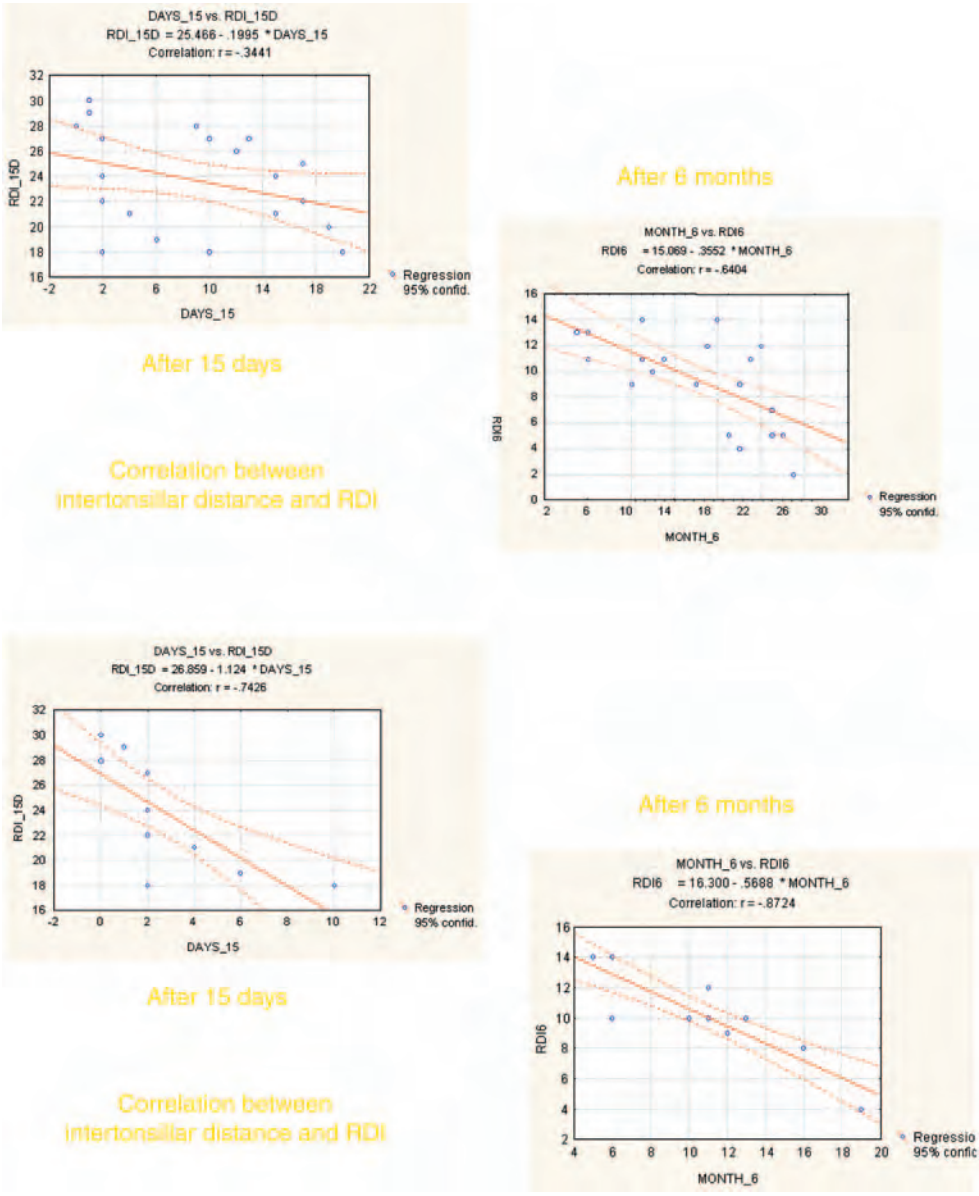


*Fig. 2.* Correlation between ITD and RDI in 20 adults (top) and ten teenagers (bottom) at 15 days (left) and six months (right) after the TVR procedure. Note that this is more significant (r) in teenagers than in adults and at the sixth month than at 15 days postoperatively.

## Conclusions

Coblation TVR, a new method that uses radiofrequency to reduce the volume of enlarged tonsils, was found to be effective and far less traumatic than traditional tonsillectomy. This method could be associated with a number of surgical and clinical advantages, including better operative results, reduced surgical time, and less postoperative pain, bleeding, edema, snoring, and fever. We think that the Coblation technique could replace, at least in selected cases, other methods of benign tonsillar hypertrophy surgery. A unique application was noted in adults and teenagers, *i.e.*, the definite improvement of nocturnal breathing in light OSAS.

A further advantage of Coblation TVR in OSAS patients is that it is performed under local anesthesia. Also, even if no hemorrhaging occurred, there may be bleeding from major vessels, and in this case we suggest puncturing the tonsil far away from its polar root. A serious disadvantage of Coblation surgery is its initial cost, although this would be reduced if it was used frequently and also by other specialists.

With regard to the TVR procedure, some questions still need to be investigated, such as: would consecutive applications make the shrinkage process more effective; can we associate TVR with surgery of other obstructed sites, thereby improving the results in more severe cases of OSAS?

We are still following up our patients, and an MRI study regarding the morphology of volumetric reduction is ongoing. We also hope to observe the histophysiological background when a tonsillectomy, needed in one of our cases, is performed in the future. Longer follow-up will also show us whether any recurrence of obstruction and/or variation in tonsil immunological behavior is likely to occur.

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# TONGUE SUSPENSION AND FURTHER SURGICAL DEVELOPMENTS FOR THE TONGUE BASE

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## Introduction

It is well known that obstructive sleep apnea syndrome (OSAS) stems from upper airways stenosis, which is very often due to pharyngeal wall and/or tongue base collapse.[1]

Widening of the anterior-posterior pharyngeal diameter can be obtained easily and effectively with a Repose™ suspension suture of the genioglossus muscle;[2,3] while the increase of the lateral diameter of the pharynx is still under investigation.

In 1984, Patton *et al.*[4] were the first to propose widening of the lateral diameter. Their technique, only tried out on animals, consists of a tri-section of the hyoid bone and separation of its three parts, which are held in place by an arch bar fixed to the bone with screws.

A different version of this technique – *i.e.*, hyoid distraction and suspension of its segments to the mandible with the Repose™ kit – has been developed separately by us[5] and by Coleman and Bick[6]; but at the present time, it has only been used in snorers by us.

The aim of the present report is to present the feasibility of a combined approach by means of tongue base suspension and hyoid distraction and suspension to the mandible with the mini-invasive Repose™ technique.

## Surgical procedure

This surgical procedure is indicated in OSAS patients with a retropalatine position of the tongue base and collapse of the lateral pharyngeal walls. Evaluation of the level of obstruction is endoscopically determined using the Müller

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maneuver and documented with NMR, while polysomnography studies are used to measure the severity of the sleeping breathing disorder.

The procedure has to be realized under general anesthesia with nasotracheal intubation. The inferior border of the mandible and of two submandibular points of insertion for the bone screws situated 2.5-3 cm laterally to the midline are identified. Only at this level can we be sure of sparing the marginal nerve, facial artery and facial vein.

Using the thyroid cartilage as a landmark, the hyoid bone is found, palpated and marked. A skin incision is made 3-4 cm in length at the superior border of the hyoid and carried down through the subcutaneous and fatty tissues and the platysma muscle. A retractor is then placed in the wound to improve exposure to the surgical site. The hyoid bone is grasped with an Allis clamp, the suprahyoid musculature is dissected, and the bone is then sectioned in the midline with a Liston wire cutter.

A submandibular incision is made at the level of the points previously identified, and the posterior surface of the mandible is exposed. The Repose™ inserter is placed into the submandibular incision and the screw positioned in the posterior surface of the mandible on both sides.

The polypropylene suture is loaded into the suture passer. The suture passer is introduced into the submandibular incision site and passed inferiorly under the subcutaneous tissues to the cervical incision, with attention being paid to preserving the anterior jugular vein.

One of the two strands of the suture is loaded on to a Mayo free needle and passed around the mid-portion of the hyoid – in a supero-inferior direction with regard to the hyoid – keeping the needle strictly in contact with the posterior surface of the hyoid bone for preservation of the lingual artery.

The suture is then tied loosely, at first, in order to see the extent of the distraction of the muscles and pharynx; once it has been decided that there is enough tension, the knot is secured and the mid-portion of the hyoid bone anchored in contact with the inferior border of the mandible.

This procedure is then repeated on the contralateral side. The final degree of lateral and posterior widening of the pharynx is verified intraoperatively with a flexible fiberscope. The meticulous contact between each portion of the hyoid bone and the mandible is usually enough to prevent the contraction of the pharyngeal muscles moving the hyoid bone medially, in that way reducing the degree of lateral widening of the pharynx.

In cases in which it is not possible to keep the hyoid bone in contact with the mandible, a second screw can be positioned, at a distance of 1.5 cm laterally from the first, and a second suture can then be used to secure the osteomuscular hyoid complex.

At the end of this surgical procedure, a drain is inserted and the incision is sutured. Genioglossus advancement and suspension are then performed with the Repose™ technique.[3] It is imperative to carry out this procedure after the hyoid procedure in order to avoid the Repose™ inserter from being infected by

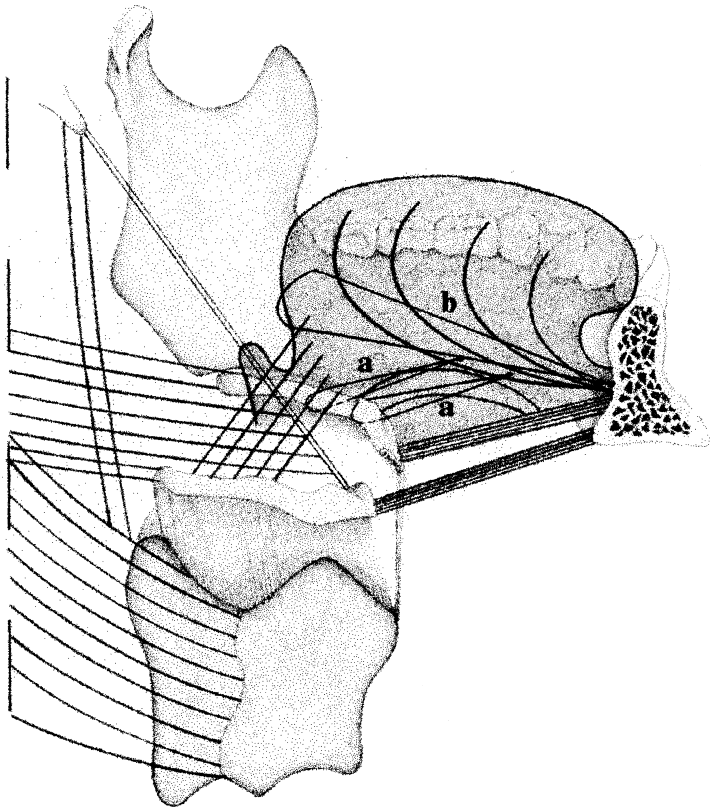


*Fig. 1.* Anchorage of the sectioned hyoid bone to the mandible (*a*) and genioglossus suspension (*b*).

the bacterial flora in the oral cavity. Figure 1 shows the two surgical combined procedures.

During the first 24-48 hours after operation, blood pressure, heart rate, respiratory rate and $O_2$-blood saturation must be monitored. Prevention of infection, inflammation and pain must also be ensured by adequate drug therapy.

## Discussion

Evaluation of the site or the mechanism of obstruction in OSAS patients is one of the most difficult tasks for specialists who study this pathology. In fact, all the different procedures available for evaluation of the level of obstruction are performed on an awake patient and are therefore categorically not representative of the anatomical situation during sleep.

The attempt to divide the mechanism of obstruction into velopharyngeal of the tongue or hypopharynx is misleading because all of these are responsible for OSAS in over 50% of patients affected by this problem.[1,7-9]

All the surgical techniques that are used nowadays for the treatment of OSAS were created to increase the anterior-posterior diameter of the pharynx, or to widen the pharyngeal space resecting the hypertrophic anatomical structures responsible for oro-hypopharyngeal obstruction.[10] Nevertheless, snoring is often also due to vibration of the lateral pharyngeal walls, and apnea is due to their collapse.

In 1984, Patton *et al.*[4] were the first to highlight the role of the lateral walls of the pharynx in the physiopathology of OSAS, and experimented with a trisection of the hyoid bone, but only in animals. In 1994, Riley *et al.*[11] proposed and performed suprahyoid musculature myotomy and suture of the hyoid bone to the thyroid cartilage, in order to decrease the degree of obstruction due to redundant lateral pharyngeal walls. Coleman and Bick[6] are studying the feasibility of expansion hyoidplasty with the mini-invasive Repose™ technique.

In our opinion, Patton *et al.*'s technique[4] cannot be performed on humans because the spongy structure of the hyoid cannot offer a stable support for a fixing mechanism with titanium bars and screws. Hyoid suspension to the thyroid cartilage, as proposed by Riley *et al.*[11], certainly widens the anterior-posterior diameter of the pharynx and reduces the folds of the lateral pharyngeal walls, increasing their tension. The final effect is also reasonable widening of the lateral diameter of the pharynx.

Our proposal of expansion hyoidplasty with the Repose™ kit causes true lateralization of the lateral pharyngeal walls of more than 1.5 cm, and anchoring and stabilizing the hyoid bone to the mandible maintain this widening in the long run.

Our technique is easy to perform, not only for surgeons who are used to dealing with this kind of surgery, but also for those who have to learn this technique '*ex-novo*'. The risk of hyoid bone necrosis is rare because the section and suture do not damage its vascularization, as already demonstrated by oncological surgery of the floor of the mouth or of the tongue[12]. Moreover, positioning of the two mid-portions of the hyoid to the mandible does not interfere with swallowing or phonation.

An unfavorable situation sometimes occurs after breaking of the polypropylene suture during traction and knotting. In these cases, it is possible to insert a second screw into the body of the mandible. We are also evaluating the possibility of using a tycron suture instead of the polypropylene one.

In our opinion, the consistency of our results, measured six months after the operation, can also be confirmed in the long term, because the precise fixation of the hyoid bone to the mandible prevents any movement or medialization, making it impossible for the lateral pharyngeal walls to collapse.

We demonstrated that this kind of operation is not only suitable in tongue base suspension, but also in other velopharyngeal surgical procedures for the treatment of OSAS, because the morbidity of the Repose™ technique is low. Therefore, we believe that this combined surgical approach should be included

in some of the many techniques for the treatment of sleeping breathing disorders due to the synchronous collapse of different anatomical sites.

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# TRACHEOTOMY AND TRACHEOSTOMY IN OBSTRUCTIVE SLEEP APNEA SYNDROME

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The surgical intervention known as tracheotomy allows, through the skin, direct communication between the trachea and the outside. Tracheostomy means an opening to the trachea through the skin.

The Aber papyrus dated 1500 BC and the later writings attributed to Asclepiades and Galenus already mentioned tracheotomy. Introduction of the tracheotomy tube is often attributed to Fabrici D'Acquapendente. And, it is thought that it was Francesco Dal Bosco who, in 1666, discovered the possibility of emitting sounds through a fenestral tracheotomy tube. In 1730, George Martine suggested the use of a double pipe, or inner cannula, facilitating the removal and cleaning of the instrument. The first descriptions of this surgical technique date back to the second century AD. In 1800, tracheotomy played a fundamental role as a solution for the ventilatory needs of the upper airway. As an innovation in surgery, in 1920 Jackson made an incision under the larynx as a way of preventing chronic laryngeal stenosis. He also upheld the necessity of appropriate hygiene for both the patient and the tracheotomy tube, thus remarkably reducing mortality and morbidity. Since that time, traditional surgical techniques have not undergone any radical changes.

Historically, tracheotomy was the first completely effective means of eliminating (by bypassing) upper airway obstructions. In the history of surgery for snoring and obstructive sleep apnea syndrome (OSAS), for many years tracheostomy represented the only surgical management capable of effectively tackling the problem of obstruction of the upper airways and digestive tract during sleep. Even today, despite the advent of nasal continuous positive airway pressure (nCPAP) and uvulopalatopharyngoplasty (UPPP), tracheostomy, in its 'skin-lined' form, still provides remarkable results in the treatment of some patients affected by OSAS.

With regard to the surgical techniques, apart from conventional tracheotomy, and particularly during intensive therapy, various percutaneous dilatation tracheostomy techniques have been developed. After pricking the anterior tra-

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cheal wall, these techniques require the introduction of a special dilatator by external means, *e.g.*, the Ciaglia type, or endoscopic means, *e.g.*, the Fantoni type. These aim at creating an opening that is sufficient to introduce a tracheotomy tube, as required by ventilation.

In the descriptive analysis of the traditional surgical technique, and as a general rule, the cutaneous incision in the neck should always be performed transversally. But, in emergency situations or particular pathologies, it might be necessary to make a vertical incision across the midline.

In the most fortuitous circumstances, the cutaneous incision is carried out within a triangular area that has the suprasternal notch as its apex, the inferior margin of the thyroid cartilage as its main base, and the mesial borders of the sternocleidomastoid (SCM) muscles as its sides. The incision must be made transversally between the second and fourth tracheal rings, and must extend from one SCM muscle to the other.

The point where the opening is made is directly related to how much time there is available. In emergency situations, the opening must be made as near as possible to the skin and level with the first tracheal rings or cricothyroid area. In cases of relative emergency, and in order to expose the laryngotracheal axis rapidly and fully, it may be necessary to perform a vertical incision. The opening of the trachea must be carried out between the second and fourth rings. In such a critical condition, tracheotomy is defined as trans-isthmus, upper-isthmus, or under-isthmus, depending on its position in relation to the thyroid isthmus. In the first instance, the isthmus is sectioned, while in the other two, it is moved. In children, it is advisable to carry out sectioning of the isthmus.

The opening made for tracheotomy is different from that made for tracheostomy. In the first case, and in adults, it is preferable to make a horizontal and inter-ring incision, while in children, it is advisable to opt for a vertical midline incision with sectioning of two or more rings. In the second case, the incision in the trachea should be made according to the type of tracheostomy. In partial tracheostomy, a skin flap is created which is attached to the trachea by a portion of the opening only, while in all complete tracheostomies the attached flap should be carried out along the whole perimeter of the opening. In total tracheostomy, full transversal sectioning of the trachea and the attached skin flap are more appropriate.

It is possible to perform these techniques under either local or general anesthetic.

The incision is made as described above. The subcutaneous tissue and the superficial layer of the deep cervical fascia, adhering to the medial cervical fascia at the linea alba, are dissected into. The anterior jugular veins are then tied and sectioned. The prelaryngeal muscles are identified, divided and retracted, while the cricoid cartilage and thyroid isthmus are exposed. The isthmus is either sectioned or, whenever possible and in order to access the space between the second and fourth tracheal rings, moved superiorly. The hemostasis is checked, and the trachea is opened using the most appropriate method.

'Skin-lined' tracheostomy is different from all other types of tracheostomy because, in this case, the tracheostomy is covered with skin during a single surgical maneuver. At the time of tracheostomy, a series of cutaneous flaps are created. These are arranged together on the tracheostomy in order to form a muff of skin. The use of this technique permits: quick stability, the prevention of granulation tissue, easy insertion or removal of the cannula, the possibility of the tracheostomy being retained without the cannula, and the new anatomical condition to be reversed.

The present requirements for the use of the 'skin-lined' technique for treating OSAS are as follows:

- OSAS with life risk and ineffectual or rejected nCPAP
- severe hypo-oxygenate (<60%)
- Severe hypercapnia
- Major OSAS-related arrhythmia
- Heart disease increased by OSAS
- cerebrovascular insufficiency increased by OSAS
- secretional ventilatory insufficiency increased by OSAS
- OSAS unresolved by other surgical techniques

Even if this surgery may appear to be easy, there are many complications due to tracheotomy. According to different cases, historical periods, levels of urgency, age, and specific or general conditions of the disease, the incidence varies from 2-50%, and mortality ranges from 0.9-4.5%.

With reference to the time of their appearance, complications can be classified as intra-surgery, early or late post-surgery, while regarding their level of seriousness, they can be major, intermediate, or minor:

- Hemorrhages during surgery have an incidence about 4%, and are mainly due to the anterior jugular vein, thyroid isthmus, and vessels such as the thyroid artery ima. Those that appear later are usually the most serious, with an incidence varying between 0.3 and 4.5%. They are exacerbated by damage to the large vessels such as the carotid artery or thyroid artery because of the progressive strain on the tracheal and peritracheal structures caused by the conflict between the cannula and trachea.
- Clinical tracheo-laryngeal stenosis does not amount to more than 4-5% and is mainly due to the prolonged presence of the tracheotomy tube. It can be classified according to its location: high-laryngeal (supraglottic, glottic), low-laryngeal or cricoideal, high-tracheal (cervical trachea), and low-tracheal (intrachest). The common pathogenetic mechanism is supposedly exacerbated by mechanical compression and serious infection. With regard to low-laryngeal and high-tracheal stenosis, surgical damage due to the tracheotomy and scratching of the cannula both contribute towards the formation of the stenosis. In high-laryngeal stenosis, insertion of the tube could be the main cause. On the other hand, the cap of the tube could be the main cause of exacerbation in low-tracheal stenosis. In order to avert these complications, a prolonged period of endotracheal intubation, tracheotomy being performed

above the second ring, and excessive removal of the tracheal wall, should all be avoided; and in children no tracheal tissues should be removed. In order to inhibit any tendency for tracheal mucosal necrosis, the cap of the tracheotomy tube should be inflated by a lower pressure than that in the endotrachea (20-30 mmHg).

- Rare (<1%) tracheo-esophageal fistulas, which are due to accidental incisions in the posterior tracheal wall or to lesions following the traumatic positioning of the tube.
- Cardio-respiratory arrest seen in patients in a serious hypo-oxygenate state or affected by chronic obstructive bronchopneumopathy with high levels of $CO_2$, due to blockage of the peripheral receptors caused by the presence of oxygen during early post-tracheotomy respiratory function.
- Damage to adjacent anatomical structures, such as the anterior wall of the esophagus, cricoid cartilage, recurrent laryngeal nerves, and pleural apices.
- Subcutaneous emphysema in 5% of patients during the first 24-48 hours. This is due to extremely large dissection of the cervical facia, coughing, or adherence of the tracheostomy tube to the tissutal planes.
- Pneumomediastinum, during the early post-surgery period, but also during surgery due to air around the trachea being expired into the mediastinum.
- Pneumothorax, with an incidence of between 0.9 and 4% in adults, and of up to 10% in pediatric patients. In patients with acute respiratory obstruction, the sudden passage of air in the lungs could cause this breakage. Prevention is aided by a post-surgery radiological check-up.
- Dislodging and/or obstruction of the tracheostomy tube.
- Infection of the tracheostomy.
- Tracheo-cutaneous fistulas.
- Infections such as tracheitis and tracheobronchitis. In infants, in their particularly serious type, *i.e.*, necrotic tracheobronchitis.
- Granulation tissue, aided by infection and by the cannula itself, since this 'behaves' like an external body.
- Precocious dysphagia associated with inhalation. This is due to reduced motility of the larynx which itself is caused by stiffness of the tube-trachea-cutaneous planes and loss of the sphinteric reflex of the glottis.

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# OBSTRUCTIVE SLEEP APNEA SYNDROME

## Anesthesiological problems

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### Introduction

Obstructive sleep apnea syndrome (OSAS) is a relatively frequent and potentially fatal pathology (the average incidence being equal to 1–4% of the adult population).[1] It is characterized by even, prolonged episodes of sleep apnea due to upper airway (UAW) obstruction. Severe perioperative complications can occur in OSAS patients, due to their extreme sensitivity to central nervous system (CNS) depressants, possible difficulties in tracheal intubation, as well as cardiorespiratory complications and the frequent presence of associated pathologies.

For these reasons, in order to understand the anesthesiological problems with regard to OSAS patients, a brief overview of the disease pathogenesis and its systemic physiopathological consequences must be taken into consideration.

### Pathogenesis of obstructive sleep apnea syndrome

During inspiration, the diaphragm normally contracts against nasal resistance. This creates subatmospheric pressure within the airways, which tends to restrict the collapsible UAW segments in oropharynx and hypopharynx.[2] In the awake subject, the tonic and phasic (synchronous with contractions of the diaphragm) activity of the pharyngeal dilator muscles (*tensor palati, genioglossus* and *geniohyoid*) counteracts the subatmospheric intraluminal pharyngeal pressure generated by the respiratory muscles, and prevents UAW collapse. The rhythmic activity of these muscles is reduced during non-rapid eye movement (NREM) sleep, and disappears during rapid eye movement (REM) sleep. Therefore, sleep fosters the recurrence of episodes of obstructive apnea, caused by

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*Table 1.* Anatomical and functional OSAS triggering factors (adapted from Boushra[2], by courtesy of the *Canadian Journal of Anaesthesiology*).

| *Altered UAW anatomy* | *Altered UAW function* |
|---|---|
| *Localized pathologies* | sleep |
| nasal obstruction | benzodiazepines |
| tonsillar hypertrophy | anesthetic drugs |
| mandibular hypoplasia | muscle relaxants |
| laryngeal abnormalities | alcohol ingestion |
| *Systemic disorders* | diabetes mellitus |
| obesity, hypothyroidism | chronic renal failure |
| acromegaly | |

the physiological decrease in muscle tone involving the pharyngeal dilator muscles, more than the respiratory ones.[3] Inspiratory obstruction mechanisms have been recognized in the anteroposterior displacement of the tongue against the posterior pharynx, in the posterior displacement of the soft palate by the tongue against the posterior pharynx, in the opposition of the lateral pharyngeal walls, and in the circular closure of the pharynx.[4] In turn, the obstruction is due to either anatomical (airway narrowing) or pathophysiological factors (incoordination of UAW dilator muscle activity) (Table 1).

## Pathophysiological consequences

Episodes of apnea followed by resumption of the airflow lead to repeated changes in blood oxygenation, autonomous nervous system tone, and acid-base balance, which have important systemic consequences. In particular, inspiratory efforts produce a vagal prevalence, which in turn leads to bradycardia, atrioventricular (AV), and sinusal cardiac block. Once the respiratory obstruction has ceased, the parasympathetic tone declines and hypoxia and acidosis lead to a sympathetic tone prevalence, causing ventricular extrasystoles and other ventricular tachyarrhythmias. Moreover, hypoxia and acidosis lead to an increase in pulmonary and systemic arterial resistances, thus causing pulmonary and systemic hypertension and, in the long run, biventricular insufficiency. A further consequence of chronic hypoxia is the stimulation of erythropoiesis, leading to polycythemia (Fig. 1).

## Effects of general anesthesia on upper airway muscle tone

Already in normal subjects, general anesthesia involves higher tone reduction in the UAW muscles rather than in the diaphragm. According to the above, this fosters UAW obstruction. General intravenous and inhalant anesthetics in par-

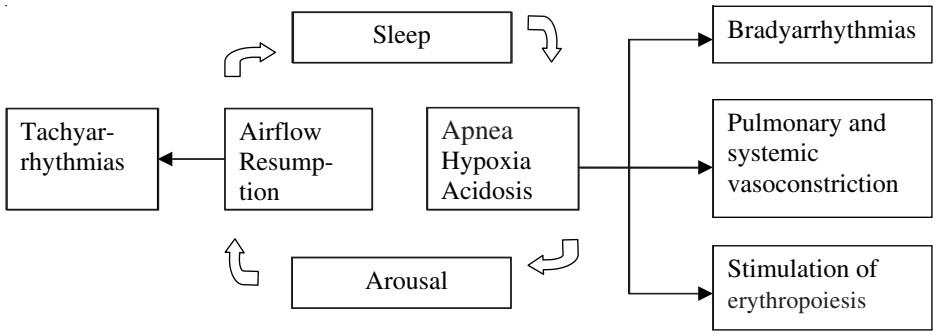


*Fig. 1.* Pathophysiological consequences of sleep apneas of anesthesiological interest.

ticular, as well as benzodiazepines, cause the selective reduction of pharyngeal dilator muscle activity. Furthermore, the UAW muscles are very sensitive to opioid analgesics and non-depolarizing neuromuscular blocking drugs (NMBDs). The induction of general anesthesia already implies a tendency for UAW collapse in the normal subject, which, since it is only partial, is usually of no consequence. This phenomenon becomes clinically evident in OSAS patients, in whom UAW collapse can cause dramatic difficulty in airway control.

## Preoperative assessment and surgical preparation

Before surgery, hypoxia and acidosis have to be pinpointed and treated. They both increase the sympathetic tone and sensitize the myocardium to catecholamines, thus inducing the possible onset of cardiac arrhythmias. Changes in the electrolytic and acid-base balance (hyperkalemia/acidosis) present in the syndrome can induce hyper/hypokinetic arrhythmias. Long-term (four to six weeks) nasal continuous positive airway pressure (CPAP) has been shown to reduce tongue volume and upper airway edema. Moreover, the pneumatic splint reduces episodes of UAW collapse and interrupts the vicious circle leading to worsening of the obstruction and systemic complications.[5] The preoperative assessment will identify patients with chronic obstructive pulmonary diseases (COPDs), and/or restrictive pathologies (Pickwick syndrome, obesity). Pickwickian patients have decreased $CO_2$ sensitivity and mechanical ventilation is probably needed when the hypoxic drive to breathe is also hindered by subanesthetical concentrations of inhalant anesthetics.

Obesity is a further risk factor due to the physiopathological modifications of the cardiocirculatory and respiratory systems, which are typical of the disease: reduction in residual functional capacity and thoracopulmonary compliance, with a shunt effect and pulmonary hypertension. The consequent hypoxia is worsened by the increase in oxygen consumption, which, in obese patients, is caused by the increased respiratory activity. Moreover, in obese patients,

tracheal intubation is more likely to be difficult. Gastroesophageal reflux and vomiting are also more frequent.[6]

Disautonomic neuropathy must be identified in diabetics (diabetes mellitus being one of the causes of altered UAW function), as this leads to arterial pressure instability and to severe hyperkinetic cardiac arrhythmias (temporal refractoriness dispersion: lengthening of the QT interval). Diabetic patients are also subject to vomiting, due to tone reduction of the lower esophageal sphincter (vagal denervation of the stomach).

Pulmonary and systemic hypertension is also assessed for detrimental effects on the right and left ventricular function. In this regard, it has been estimated that there is approximately a 30% prevalence of sleep apnea syndrome in patients affected by ischemic cardiopathy, and that this worsens the coronary risk, inducing coronary spasm.[7]

Polycythemia (hematocrit > 55%) must be treated in order to improve cerebral blood flow and to reduce the risk of thromboembolic phenomena.

The chronic use of antihypertensives, cardiokinetics, diuretics, and antidepressants has to be considered for their effects on the cardiocirculatory system and their possible interference with anesthetics (tricyclic antidepressants deplete noradrenaline from the nerve endings, which become hypersensitive to catecholamines). Due to their sensitivity to CNS depressants, and in particular to opioid analgesics and benzodiazepines, these drugs should be banned from anesthetic premedication in OSAS patients. An anticholinergic agent should be administered in order to contrast the bradycardiac effects of anesthetics and laryngeal stimulation.

## Induction of anesthesia

The induction of general anesthesia and airway control are very delicate in OSAS patients. In fact, due to these patients' extreme sensitivity to CNS depressants, once the unconscious state has been reached, the anesthesiologist will encounter many difficulties in controlling airway and pulmonary ventilation if UAW dynamic collapse occurs. Associated pathologies, *i.e.*, tonsillar hypertrophy, laryngeal abnormalities, mandibular hypoplasia, obesity, diabetes mellitus, etc., increase this risk, due to possible difficulties in laryngoscopy and tracheal intubation. The use of non-depolarizing NMBDs can hinder airway control, given the higher sensitivity of the UAW muscles to these drugs rather than to ventilatory ones.

There are two possible strategies to minimize the risk of hypoxia:

1. A rapid induction-intubation sequence, using short-acting anesthetic and depolarizing NMBDs (succinylcholine): in case of failure, the short-lasting action allows the rapid return to spontaneous ventilation.
2. Tracheal intubation with local anesthesia, using fiberoptic instruments, or induction with an inhalant anesthetic, avoiding muscle relaxants.

The latter technique is the procedure of choice when the preoperative assessment has pinpointed a possible difficult intubation. In any case, adequate preoperative oxygenation will reduce the risk of hypoxia in this phase. If UAW obstruction develops during induction, an attempt should be made to relieve this by optimizing head-jaw positioning and/or by using oropharyngeal and/or nasopharyngeal devices.

## Maintenance of anesthesia

In order to ensure the patient's safety, it is essential to proceed with controlled pulmonary ventilation once tracheal intubation has been performed. This guarantees adequate gas exchange. Despite controlled ventilation, hypoxia is a constant danger in obese patients. General anesthesia and the position on the operating table worsen the respiratory effort and result in an intrathoracic increase of the blood volume. This aggravates the shunt effect and the consequent hypoxia. Cardiorespiratory anomalies are more remarkable in Pickwick syndrome patients, covering a combination of serious obesity, sleepiness, periodic breathing, alveolar hypoventilation, polycythemia, and right ventricular hypertrophy.

Without prejudicing the priority of blood oxygenation, while normocapnia has to be obtained in OSAS patients, preoperative $PaCO_2$ must be maintained in Pickwickian, hypercapnic patients. In the latter, $PaCO_2$ reduction has been shown to cause both sleep apnea and postoperative hypoxemia. Moreover, arterial $PaCO_2$ normalization could lead to severe metabolic alkalosis. Chronic hypercapnia implies renal conservation of bicarbonate and, pH being determined by the $[HCO_3^-]/PaCO_2$ relationship, $PaCO_2$ lowering will result in an increased pH. Even if $PaCO_2$ is reduced slowly, the patient may continue to be alkalotic, since the renal excretion of bicarbonates is not as fast as $PaCO_2$ lowering in the blood. Such alkalosis can cause seizures.[8]

The use of rapid elimination volatile agents (sevoflurane > halotane > isoflurane) is required to maintain anesthesia. Nitrous oxide could be useful due to its low lipid solubility; nevertheless, its use is restricted due to the hypoxic risk and the presence of pulmonary hypertension. The extensive use of intravenous anesthetics is limited by their lipid solubility and accumulation possibility, especially in prolonged administration. In any event, these drugs should be used at the minimum effective dose, and the short-acting ones are to be preferred.[9] With regard to opioid analgesics, their use should also be kept to a minimum and to those with the most rapid kinetics. In fact, it is well known that the long-lasting effects of these drugs are related to postoperative respiratory problems. In this phase, the use of competitive intermediate-duration NMBDs (atracurium and vecuronium) is preferable to longer-acting relaxants. Their duration of action is predictable and any eventual residual effects can be counteracted by an anticholinesterasic agent.

## Postoperative period

The postoperative period is definitely more dangerous in OSAS patients. Given their high sensitivity to CNS depressants, the residual action of anesthetics, benzodiazepines, opioid analgesics, and curarizing drugs can lead to acute airway obstruction.[10] This can occur precisely when the attention of the nursing staff drops, wrongly assuming that the danger has been overcome. The following recommendations are suggested: caution should be exercised when using these drugs; a cautious choice of agents should be made regarding the most rapid elimination kinetics; specific antagonists should be used after surgery, and the vital functions of these patients should be checked for a much longer time than of patients under normal general conditions. In the postoperative period, the sitting position enhances gas exchange, thus reducing apneic episodes. This is particularly true in obese patients. With regard to postoperative analgesia, opioid analgesics are counterindicated, and the use of regional anesthesia or non-steroidal anti-inflammatory drugs is preferable. There is no unanimous agreement on the routine use of supplemental oxygen in the postoperative period. Dangerous episodes of hemoglobin desaturation can be prevented by $O_2$ administration. Nevertheless, the correction of hypoxia can delay sleep arousal and airflow resumption, with persistence of apnea. Moreover, in Pickwickian and hypercapnic patients, $PaO_2$ normalization can further reduce alveolar ventilation, causing catastrophic respiratory insufficiency. Oximetry monitoring,

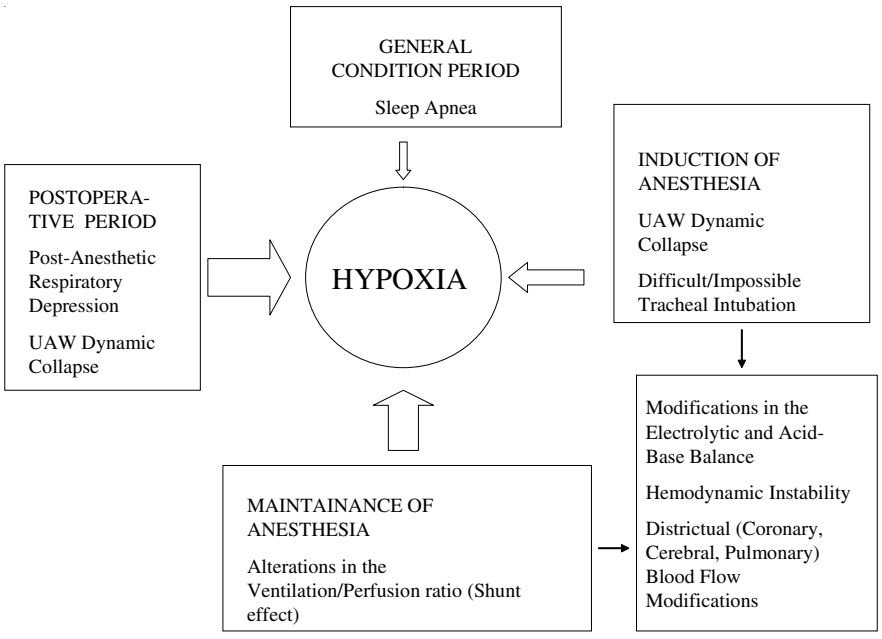


*Fig. 2.* Consequences of anesthesia on pulmonary gas exchange, electrolytic and acid-base balance, systemic and pulmonary hemodynamics (see text for details).

frequent $PaCO_2$ artery measurements, and careful and lasting clinical control, will direct the choice towards the most valid method.

In conclusion, OSAS is a pathology with one of the highest anesthesiological risks. Hypoxia represents the greatest danger, being the main cause of cardiocirculatory arrest. Already existing before surgery, hypoxia can be dramatically worsened by general anesthesia, in all its phases, with the immediate postoperative period representing the greatest risk (Fig. 2).

Other risk factors are as follows:

1. Possible modifications in the electrolytic and acid-base balance (hyperkalemia/acidosis, hypokalemia/alkalosis), with consequent alterations in the electric balance of the myocardial fiber membrane, as well as cardiac hypo/hyperkinetic arrhythmias.
2. Endangering systemic and pulmonary hemodynamics.
3. Modification of the local coronary (myocardial ischemia), pulmonary (alteration of the ventilation/perfusion ratio), and brain (seizures) blood flow.

Only a greater knowledge of the mechanisms responsible for each alteration, and the experience achieved in the management of these patients, will overcome the catastrophic consequences caused by anesthesia.

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# HIGHLIGHTS ON SURGICAL THERAPY

# HYOID POSITION CORRELATES WITH RESPIRATORY EVENTS AND PULMONARY FUNCTION IN OBSTRUCTIVE SLEEP APNEA PATIENTS

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## Introduction

Obstructive sleep apnea (OSA) is a disorder in which recurrent closure of the upper airway occurs during sleep, generally at the level of the oropharynx.[1] The common symptoms of obstructive sleep apnea syndrome (OSAS) are hypersomnolence, headaches, intellectual deterioration, depression, and severe anxiety. OSA patients are frequently hypertensive and may exhibit signs of cardiac diseases. Several studies have analyzed the correlation between the clinical features and the cephalometric and otorhinolaryngological variables in OSA patients. The patency of the upper airway is a result of many interrelated anatomical and physiological factors.[2]

Abnormal cervico-cranial morphology has been reported, including an elongated soft palate, inferiorly positioned hyoid bone, decreased sagittal dimension of the cranial base, macroglossia, retrognathism, mandibular micrognathia, increased anterior size of the bony pharynx and deviation of head posture.[3-4]

Hyoid bone caudalization has been correlated with an increased apnea-hypopnea index (AHI) and with obesity.[5] We investigated the correlation between hyoid position, respiratory events and pulmonary function.

## Methods

We studied 66 patients (40 males and 26 females; age range, 35-50 years; mean age, 45 years). All patients had a history of disturbed sleep, characterized by heavy snoring and recurrent apneic periods, as well as excessive day-

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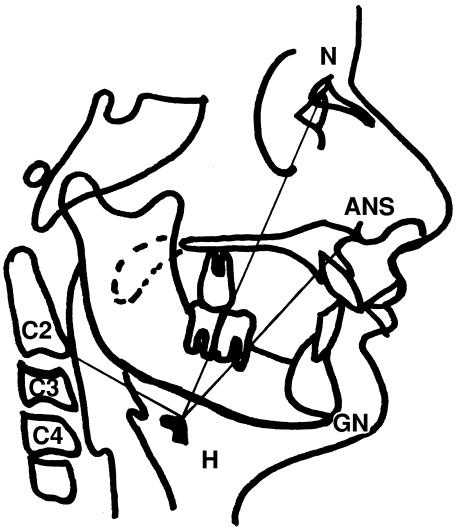


*Fig. 1.* Diagram showing cephalometric measurements.

time sleepiness. The control group consisted of 11 healthy adults (six males and five females; age range, 34-50 years; mean, 46 years). The body mass index (BMI, weight kg/height $m^2$) was calculated for each patient.

All subjects underwent a physical evaluation, including head and neck and neurological examinations, and pulmonary and cardiac function tests. All-night polysomnographic recording documented the presence of OSA in all patients. The sleep recording included inductive plethysmography, abdominal and thoracic respiratory movements, and oxygen saturation using pulse oximetry (Somnostar PT, Sensor Medics). Lateral cephalometric radiographs were performed in all patients using the technique described by Riley *et al.*[3] The cephalometric measurements included the distance between the hyoid anterosuperior edge (H) and *(a)* the antero-inferior margin of the second cervical vertebrae (H-C2), *(b)* the nasion (H-N), *(c)* the anterior nasal spine (H-ANS), *(d)* the gnathion (H-Gn), and the angles between C2-H-N and C2-H-ANS (Fig. 1).

The mixed-obstructive AHI (AHIO) and mean ratio of tidal mid-inspiratory and mid-expiratory flows (IE50) were obtained by inductive plethysmography. Statistical analysis was performed using the ANOVA test, linear regression analysis and multiple regression analysis.

## Results

The results of cephalometric analysis of the 66 patients and 11 control subjects are summarized in Table 1. The hyoid bone was found to be caudally displaced in the apnea patients compared to the control group, with a highly significant

*Table 1.* Results of cephalometric analysis in patients and controls

| | *Controls* | *OSA (all)* | *OSA (BMI>27.9)* |
|---|---|---|---|
| H-C2 (mm) | 40.2 ± 4.3 | 50.9 ± 6.8 ($p$=0.0045) | 46.6 ± 5.6 ($p$=0.002) |
| H-ANS (mm) | 86.5 ± 6.9 | 103.4 ± 11.8 ($p$=0.004) | 108.3 ± 11.6 ($p$=0.006) |
| C2-H-N (degrees) | 82.7 ± 12.2 | 72.6 ± 7.9 ($p$=0.0013) | 71.0 ± 7.7 ($p$=0.06) |

greater distance from the anterior nasal spine to the hyoid (H-ANS) from the second cervical vertebrae to the hyoid (H-C2), and from the nasion to hyoid (H-N), with smaller C2-H-N and C2-H-ANS angles even after exclusion of the 26 most obese subjects (BMI>27.9).

On multiple regression analysis, after adjustment for age and BMI, increased H-C2 distance predicted *(a)* more severe nocturnal and daytime hypoxia ($F = 12.4$ and $F = 7.4$, with $p < 0.01$) and *(b)* lower values of FVC and FEV1 (percentage predicted; $F = 30.5$ and $F = 21.6$, with $p < 0.01$). IE50, an index of sleep-related inspiratory airflow limitation, showed a negative correlation with H-Gn ($F = 17.1$, with $p < 0.01$). These indexes did not predict AHIO in our study.

## Discussion

Skeletal craniofacial and soft tissue abnormalities of the upper airways have been frequently reported in patients with OSA.[3,4,6-8] These abnormalities predispose patients to pharyngeal occlusion and are related to the severity of OSA.[5,6] One of the most studied types of cephalometric data in OSA patients is the low position of the hyoid bone.[3,6,9,10] The position of the hyoid bone is limited by vertebral development and should be at the C3-C4 level by three years of age, and at C4 by adulthood.[4,9] However, there is an abnormally low hyoid position in OSA patients. Usually, in cephalometric measurements, the position of the hyoid bone is calculated with respect to the anterior nasal spine and the gnathion. Instead, we found a highly statistically significant increase in the distance between the hyoid bone and the second cervical vertebrae (H-C2), which is considered to be a less variable anatomical parameter than other cephalometric points.

The increased H-C2 distance retained a statistically significant value role even after exclusion of the most obese subjects. This suggests that a low hyoid position may be considered to be a marker of airflow limitation in OSA patients, which is not otherwise explained by age or BMI. Moreover, our results seem to confirm that palatal surgery alone may not be adequate for the treatment of OSA.[11-13]

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# THE USE OF A MICRODEBRIDER OR SHAVER IN SNORING AND OBSTRUCTIVE SLEEP APNEA SYNDROME

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## Introduction

Obstructive sleep apnea syndrome (OSAS) is a disorder in which there is intermittent cessation of the airflow during sleep, caused by a temporary obstruction in the upper airway. OSAS is defined as 15 or more episodes of apnea (cessation of airflow for > 10 seconds) or hypopnea (reduction of airflow by 50%) per hour of sleep. It is classified as mild, moderate, or severe, according to the number of apneas or hypopneas per hour of sleep. OSAS can be due to an obstruction at any level of the upper airway. Upper airway size is determined by soft tissue and skeletal relationships, which are the major determinants of the patency of the upper airway during sleep.[1,2] Most patients with OSAS have redundant tissue or an abnormally small air passage. These anatomical variants associated with muscular relaxation during the deeper stages of sleep, and with negative pressure within the upper airway during inspiration, can cause the upper airway to collapse, resulting in obstruction of the airflow.[3] Because increasing nasal resistance results in an increase in negative oropharyngeal pressure during inspiration, nasal obstruction can also predispose to upper airway collapse.[4]

Nasal obstruction has frequently been mentioned to be a possible risk factor for OSAS,[5] and its surgical management has been reported to be effective in the treatment of OSAS in patients without craniomandibular abnormalities.[6] However, other studies using objective nasal resistance measurement did not find that nasal obstruction was a risk factor for OSAS, and they observed that nasal surgery only has limited efficacy for sleep apnea, as defined by the above criteria, but significantly improves sleep quality and daytime sleepiness.[7,8] Nasal

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obstruction does not represent the only cause of snoring, but it substantially contributes to its worsening.

The principal causes of nasal obstruction can be improved surgically using either local[9] or general anesthesia. This chapter provides a description of the mechanism and application of microdebriders in this condition.

## The microdebrider

### *Brief history*

The microdebrider is a power rotary instrument which is used almost routinely in endoscopic surgery for nasal obstruction.

This powered device was originally used by Urban and House in the endocranial reduction of acoustic neuromas in the early 1970s (the so-called 'Cavitron', patented under the name of 'power rotary dissector').[10,11] Then in the late 1970s, a modified instrument, going by the name of 'shaver', was used in arthroscopic surgery of the knee, shoulder, and temporomandibular joint (TMJ). Finally, in 1994, Setliff and Parsons introduced a powered rotary shaving device with suction called a 'Hummer' microdebrider, which could be applied in endoscopic sinus surgery (ESS).[12] They postulated that this was a safe and effective instrument for ESS[13] in both a private practice setting and in a university otolaryngology residency program.

### *Technical features*

The microdebrider (Fig. 1) is made up of:

1. A digital electronic console (power unit) of different sizes and shapes, which controls the rotary speed of the blades, aspiration, and irrigation.
2. A handpiece (straight or 90° angled) with a rotary power of up to 6000 rpm.
3. A foot switch operated by the surgeon.
4. Two sterile, disposable cannulas with blunt tip and lateral port, as follows:
   a. a stationary outer cannula, 2-4 mm in diameter and ±8 cm in length, with a blade-cutting lateral window;
   b. an oscillating or rotating inner cannula with a lateral port which cuts and extracts the soft tissue suctioned through the port of the cannula. (The sharp inner blade cuts the suctioned soft tissue against the sharp outer blade.) The inner cannula can also be displaced by a drill with a lateral protective sheath.

The serrated cutting edges cut the pathological tissue, and the soft tissue is suctioned into the lateral port. Accelerated healing, with the consequent reduction of crusts and synechiae, occurs if some normal tissue is left, which is not possible during excisional surgery.

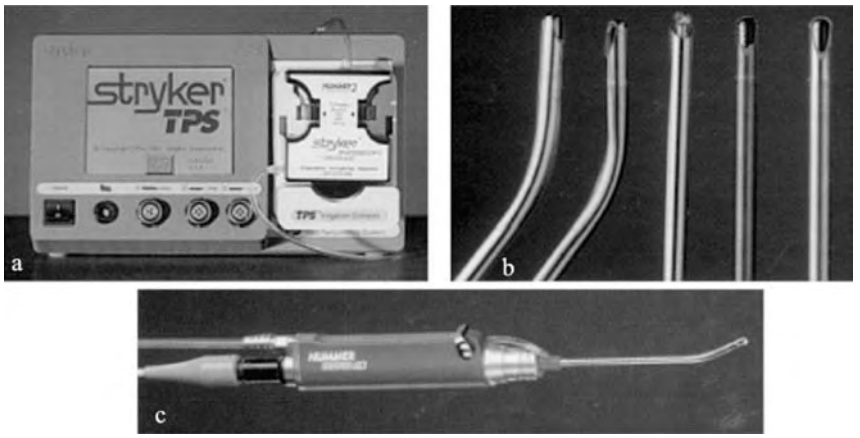


*Fig. 1.* Components of the microdebrider (the Hummer TPS model from Stryker). *a.* Digital electronic console with a touch screen. *b.* Different types of blades and burrs. *c.* Ergonomic, straight handpiece (with angled blade).

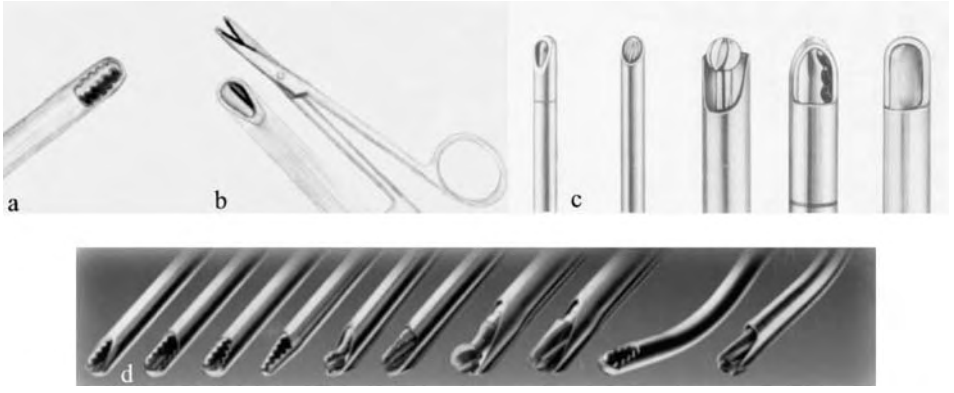


*Fig. 2. a.* Guillotine-type cut. *b.* Scissor-type cut. *c. and d.* Various kinds of blades and burrs.

The tip of the instrument is blunt, thus reducing trauma at the nasal weak points: fovea, lamina papyracea, lamina cribrosa, and sphenoidal sinus structures. This avoids the complications of CSF leakage and cerebral, neurovascular or orbital tissue damage. Bony tissues, especially lamellae and septa, are removed with either a double smooth-edged window blade or an internal drill with a lateral distal sheath.[14]

The different angles between the outer and inner windows determine the type of cutting. If an inclined outer window with a straight inner window is used, a scissor-type cut is made (Fig. 2b). This is indicated for bony tissue. For a pinpoint cut (especially with smooth edges), a straight outer and inner window is used, giving a guillotine-type cut (Fig. 2a). This is indicated for cutting

and extracting soft tissue (especially with aggressive serrated edges). At the tip of the microdebrider, a burr with a lateral protective sheath can also be used to drill thick bones, thus avoiding mucosal injury (Fig. 2c).

The rotational speed of the inner blade, combined with the area and shape of the outer window, determines the size of the fragments of tissue. Aspiration in the inner cannula is facilitated by irrigation with physiological solution, between the two cannulas (reducing clogging and obstruction of the inner tube).[9,10,15,16]

The main problem with microdebriders is the capital outlay, especially with the new generation instruments with their computerized consoles, used not only in nasal, but also in plastic, maxillofacial, and otological surgery. The wide range of disposable blades and ends also makes them expensive.

## Additional instruments

As in all endoscopic sinus surgery procedures, knowledge of the nasal anatomy is fundamental for success. This is improved by the use of 0-45° rigid scopes and CT or MRI. In the last few years, these devices have been combined in the so-called 3-D Navigation (Fig. 3), a software-integrated system which localizes the tip of the instrument in the nasal structures, integrating the CT or MRI images with the endoscopic view, intraoperatively and in real-time, allowing surgical procedures to be performed with precision and safety.

Before resorting to the use of a microdebrider, we should not forget other less expensive instruments such as radiofrequency devices,[17] traditional forceps (with or without suction), and modified through-cutting forceps. For ex-

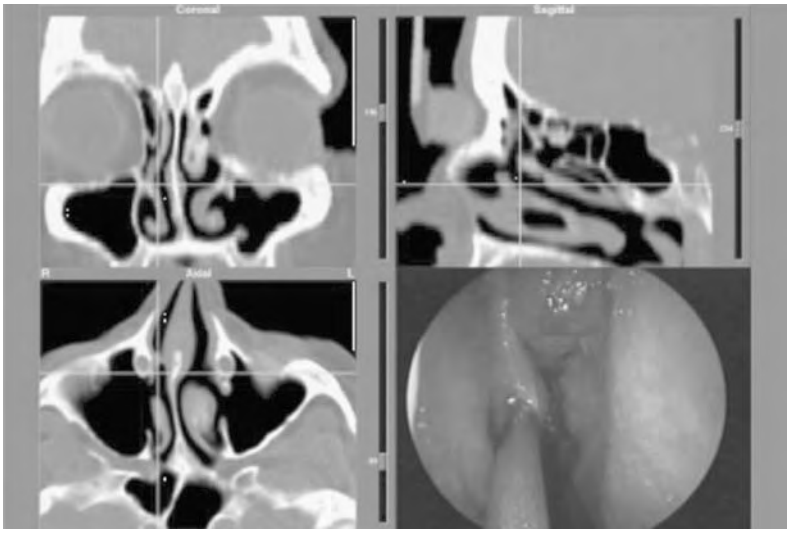

*Fig. 3.* The 3-D navigation system: the tip of the instrument is well localized in the coronal, axial and sagittal planes, combined with a direct endoscopic view.

ample, in order to remove bulky polyps, not possible to be reduced with topical vasoconstrictors, it is better to use large Weil or Blakesley-Weil 0°-45°-90° forceps or a radiosurgical device such as Ellman's radiosurgical Snare.

Resection of bone septa or lamella with pathological mucosa, which sometimes blocks drainage of the sinusal cavity, can easily be performed with the punches and through-cutting forceps modified by Herrmann, Struycken, Moriyama and Wigand.[18]

The cavernous body of the turbinates can be reduced by the radiofrequency bipolar handpiece, with fewer complications being incurred than with lasers, cryotherapy, or the 2.0/2.9-mm turbinate blade of a microdebrider.[19-21]

When widening the ostium of the maxillary sinus, scarifying the fontanella, we prefer to use Stammberger's retrograde forceps; this instrument allows the mucosal margin of the ostium to be preserved with correct healing, with no re-occlusion.

The microdebrider must never be pushed into deep structures, especially when it is being used with aggressive blades or burrs, and it is essential to preserve the principles of safe resection of the bony lamina (such as the bulla ethmoidalis and sphenoidal septa). The cutting tip must never be turned towards the lamina papyracea, because trauma to or fragmentation of the lamina results in aspiration, not only of the bone, but also of the orbital tissue, with probable injury to the medial rectus muscle.[22]

Angled blades should be carefully managed, by an experienced specialist and with accurate localization of the tip of the instrument, especially when they are being used on adenoid tissue[23] or in the sino-nasal recesses.

It is thought that, in the correction of upper airway obstructions, such as polypoid degeneration of the inferior turbinates, nasal polyposis, and choanal atresia, the microdebrider is to be preferred for reasons of safety, more rapid healing, less bleeding, and reduction of crust formation, despite the capital outlay and resource costs.

Recently, microdebriders have been used in the resection of adenoid tissue, in soft palate surgery, and in OSAS patients when performing uvulopalatoplasty (UPP). Tarabichi describes a technique of microdebrider-assisted UPP and compares this with $CO_2$ laser uvulopalatoplasty (LAUPP).[24] He suggests the use of the microdebrider as an alternative to the laser on the grounds of cost if less than 50 procedures are performed in an office setting. He also highlights the compact size of the equipment, the safety of the patient, surgeon and medical staff, the reduction of postoperative pain and swelling, less bleeding, and the possibility of a further operation to improve the functional result.

## Comparison between various microdebriders

Several authors have compared the technical features and performance of various microdebriders available commercially (Fig. 4).


*Fig. 4.* Various types of microdebriders available commercially. *a and b.* The XPS Straightshot from Xomed (nowadays Medtronics). *c.* The XPS 2000 from Xomed. *d.* The ESSential Shaver from Smith and Nephew, Memphis. *e.* The Turbo 7000 from Smith and Nephew, Memphis. *f.* The Stammberger microdebrider from Storz. *g.* The Hummer II microdebrider from Stryker. *h.* The Hummer TPS from Stryker.

Bhatt[25] compared the Hummer II from Stryker, the Linvatec, the ESSential shaver from Smith and Nephew ENT Inc., and the XPS Straightshot from Xomed (nowadays Medtronics), and concluded that there were all satisfactory in terms of mucosal preservation, less traumatic surgery, clear visualization of the operating field, reduction of the duration of surgery, and faster healing.

Ferguson *et al.*[26] tested six different microdebriders using a standardized soft tissue model (fresh raw oysters, excluding muscle) and a firm tissue model (fresh raw oyster muscle), and also a model representing the lamina papyracea (eggshell) and dura (egg sac). The efficacy of the different instruments was measured in grams of tissue aspirated per minute. These authors tested the Straightshot (4.0-mm blade) from Xomed, ESSential Shaver (Smith and Nephew, Memphis, TN; 4.0-mm blade), Linvatec (4.2-mm blade), Dyonics (3.5-mm blade), Wizard Plus (4.0-mm blade), and Hummer II from Stryker (4.0-mm blade). The Xomed Straightshot (4.0-mm blade) was statistically superior to all other microdebriders in terms of efficiency of aspiration in the firm tissue. All the microdebriders were able to abrade a ‘bony’ spicule and an intact ‘dura’, whereas none could abrade intact ‘bone’.

Setliff and Parson (personal communication) compared the Hummer II from Stryker (nowadays known as the Hummer TPS) with the Linvatec and Xomed Straightshot. The Hummer offered good handling, and better irrigation and aspiration, and due to its greater speed (6000 rpm in rotation and 3000 rpm), a more precise cut.

Stammberger has designed a new model of a microdebrider for Storz. This incorporates more powerful aspiration and an ergonomic handpiece angled at 90°, but no irrigation.

## Conclusions

The microdebrider is a useful surgical instrument, not only in the surgical management of nasal obstructions associated with snoring and OSAS, but also in the resection of adenoid tissue, and in uvulopalatopharyngoplasty. It enables rapid and efficient surgery, more precision, and greater safety. This is not only because of the direct and clear endoscopic view of the operative field, but also because of its cutting and suctioning action. The use of a microdebrider reduces intra- and postoperative bleeding and produces a rapid healing process, with the reduction of crust formation.

In conclusion, our experience after six years leads us to agree with other authors that the microdebrider represents a significant advance in surgical instrumentation. It is a simple adjuvant for helping patients who are suffering from snoring and OSAS to achieve a better quality of life, even if their underlying problems are not cured.

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# UVULOPHARYNGOPALATOPLASTY ACCORDING TO KAMAMI WITH THE DIODE LASER IN PATIENTS SUFFERING FROM SNORING

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## Introduction

Snoring is a low-frequency respiratory noise, from 60-100 Hz, with an elevated intensity of 70-80 dB HL. The noise is created by the soft structures of the upper airways vibrating during sleep. These vibrations are a consequence of increased activity in the respiratory muscles, diaphragm and intercostal muscles. Consequently, this causes an increase in endothoracic pressure of up to ten times its normal value (5-10 mm $H_2O$). Snoring could therefore be a sign of an obstruction in the upper airways, or a sign of the rather more complex obstructive sleep apnea syndrome (OSAS). OSAS may be diagnosed when the respiratory disturbance index (RDI) obtained during polysomnographic recording is above 15.

OSAS may also be diagnosed when other symptoms are manifested, such as diurnal drowsiness, behavioral and cognitive disturbances such as headaches, early morning dizziness, impotence, diurnal and nocturnal enuresis, and attacks of dyspnea, or alternatively, alveolar hypoventilation or arterial hypertension.

The most common causes of obstruction are as follows: adenotonsillar hypertrophy, deviations of the nasal septum and pyramid, hypertrophy of the soft palate or of the base of the tongue, loss of muscle tone in the pharynx, cranial and facial malformations, etc. Therefore, the role of the diagnosis is to locate the area responsible for the obstruction and to carry out the appropriate surgical correction. From consideration of the literature and our own experience, we can state that laser-assisted uvulopalatoplasty (LAUP) is suitable for less than 30% of snorers, and that, of this group, 80% benefit from this type of operation.

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## Material and methods

From 1994 to 1996, we studied 150 patients who suffered from snoring, but only performed 50 LAUP operations. Of these 50 patients, 47 were male and three female, and were aged between 45 and 65 years (average age, 54 years). Diagnostic screening included the following assessments:

First of all, we performed rhinopharyngoscopy with Müller's maneuver. This consists of forced inhalation with the mouth and nose closed, first in a sitting position and then lying down. We carried out this procedure even though we were aware that it is only considered valid for predicting the suitability of LAUP by a few authors (*e.g.*, Sher *et al.*[1]).

For the second assessment we employed active anterior rhinomanometry, in order to exclude patients with nasal stenosis whose comprehensive normal values were between 0.2 and 0.3, with nasal resistances recorded at 150 Pascal.

Thereafter, we carried out cephalometry X-rays to evaluate the tongue space index (*i.e.*, the relationship between the area of the tongue mass and the area of the oral cavity) and the mandible-hyoid angle (the angle between the line that joins the gnathion to the gonion and the line that joins the gnathion and the hyoid bone to the vertex on the gnathion).

Subsequently, polysomnography with the Eden Trace II Plus was performed in order to obtain information about $PO_2$, cardiac frequency, and the number of hypopneas and/or apopneas occurring during sleep. Hypopnea is when the inspiratory flow decreases by 50% for periods of at least ten seconds, with a 40% decrease in oxygen saturation; apnea is when breathing pauses last for at least ten seconds. The most important information obtained during this examination is the RDI, or rather, the relationship that occurs between apnea and hypopnea during the recording, because this allows us to distinguish between the classic snorer, with an RDI of less than 15, from a patient with OSAS, with an RDI of more than 15.

Finally, we carried out neurological and pneumological evaluations.

The patients who were selected in this way underwent LAUP operation with the diode laser, according to Kamami.[2] Forty-one patients were operated on under local anesthetic and the remainder under general anesthetic. The reasons for general anesthesia were as follows: in two patients because they refused local anesthesia; in two because of strong pharyngeal reflexes; in three because of macroglossia; in one because of a reduced mouth opening; and in one because of a short, fat neck. Examinations were performed one, three, six, and 12 months after operation, and included the patients' own evaluations of their degree of diurnal drowsiness and interviews with the patients' partners to determine the level of disturbance caused by the patients' snoring during the night. The examinations also included polysomnography in order to objectively evaluate the information contained in the parameters mentioned.

## Results and discussion

The uvulopharyngoplasty operation proposed by Ikematsu in 1964[3] and expanded by Fujita *et al.* in 1981[4] to resolve classic snoring by hypertrophy of the soft palate, has undergone numerous variations: by Simmons in 1984,[5,6] Fairbanks in 1984,[7] Djupesland *et al.* in 1987,[8] Dickson and Blokmans in 1987,[9] and Meyer *et al.* in 1988,[10] etc. However, none of these methods was very successful due to the patients' low tolerance, and to the long hospitalization times involved.

The use of lasers, in particular the $CO_2$ and the diode, together with the better knowledge of the physiological anatomy of the oropharynx and the hypopharynx, have allowed us to remedy these two major drawbacks, and perhaps also to better control the fields for LAUP application by means of adequate diagnostic screening.

The epidemiological data collected in our cases do not differ much from the data collected on a larger scale by Lugaresi *et al.*,[11] according to which there is a major prevalence of male patients up to the age of 50 years, while the same pathology is easier to find in female patients during and after the menopause. Potential co-factors, such as obesity, age, smoking, and drinking, were present in 60% of cases. However, correcting these habits by dieting or reducing the intake of cigarettes and alcohol showed a major improvement of symptoms in only four patients.

Forty of the 50 patients (80%) who underwent LAUP operation with the diode laser were completely cured of snoring. In the remaining ten patients (20%), we only observed a slight improvement, which we think can be attributed to the concurrent presence of obstructive joint causes, which were afforded little importance during the diagnostic screening, rather than to an unsuccessful surgical technique. In this subgroup of patients, accurate monitoring has already been commenced in order to ascertain whether a similar situation might develop with OSAS. This would make it necessary to resort to methods such as continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP) in order to avoid complications arising that are typical of the pathologies we have reviewed.

Two patients reported side-effects: posterior rhinolalia in one case and disturbances in swallowing reflex coordination in the other, both of which resolved spontaneously after two and three months, respectively.

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# NASAL RESPIRATORY FUNCTION AFTER PYRAMID SURGERY

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## Introduction

Nowadays, reductive rhinoplasty represents the vast majority of corrective nasal pyramid surgery. Following rhinoplasty, nasal obstruction is clinically suspected as being an important functional sequela in many patients undergoing this procedure. From personal experience, many surgeons would support the belief that little or no deterioration occurs in the nasal airflow in this group of patients. Before performing this cosmetic procedure, the surgeon must consider the ethical and legal implications, since it is important to realise the physiological effects following aesthetic rhinoplasty on a normal functioning nose. Nasal airflow has been studied extensively following cosmetic rhinoplasty, but there has been no evidence that this alters significantly after surgery.[1,2]

The main focus of studies presented so far in the literature has traditionally been 'the respiratory function' of the nose, thereby assuming that other functions (heating, olfaction, phonation) are minimally affected in the process. Reduction rhinoplasty usually involves the excision of an osteocartilaginous hump, with a lateral osteotomy being mandatory to close the 'open roof'. For aesthetic reasons, a low-approach lateral osteotomy is recommended by many authors,[3,4] in order to avoid a step deformity. Since lateral osteotomy starts at the pyriform aperture, many authors were particularly interested to investigate the effects on the nasal airflow caused by surgery on this anatomical structure,[5,6] which is, in fact, an integral part of the nasal valve system. Webster *et al.*[7] introduced the curved lateral osteotomy technique to protect airway reduction; Bussi and Amasio[8] noted unaltered nasal flow in a group of 30 young subjects undergoing aesthetic rhinoplasty; Adamson *et al.*[1] reported not having

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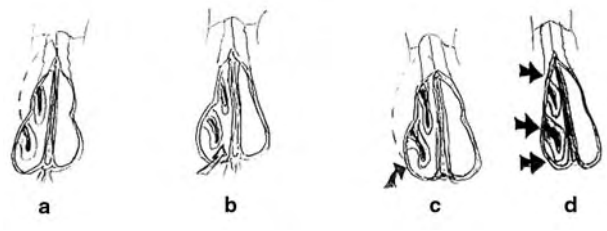


*Fig. 1. (A)* If the lateral osteotomy is started very inferiorly, medial displacement of the inferior portion of the piriform aperture can result in iatrogenic nasal obstruction *(B)*. *(C)* Starting the osteotomy higher allows good nasal narrowing without airway compromise *(D)*.

*Fig. 2.* The correct curve of lateral micro-osteotomies following a 'high to low to high' line, using a percutaneous approach and a 2-mm osteotome.

found any significant subjective or objective changes, despite the potential for a decreased cross-sectional area of the valve region.

An important prerequisite in the choice of the correct fracture line is that, along the nasal pyramid, sections can be performed that represent equilateral triangles descending from the base towards the root of the nose, and therefore, when performing lateral osteotomy, this architecture must be respected.[9] To this end, the level of the lateral osteotomy is a very important point to be considered in order to obtain adequate aesthetic results while, at the same time, avoiding unwanted narrowing of the nasal valve (Fig. 1). Indeed, during a rhinoplasty procedure, careful preoperative evaluation and planning is indispensable to the surgeon, in order to maximize the best aesthetic result, while preserving nasal functionality.[10] Based on these premises, when performing osteotomies, different fracture lines have been adopted over time: the rectilinear vertical

line that meets the transverse osteotomy at a 90° angle, and the vertical oblique line, both follow a 'low to high' line; while the vertical curvilinear line[11] follows a section line defined as 'high to low to high'.[10]

On the basis of the above considerations of clinical and functional order, the general consensus is that the safest choice for performing lateral osteotomies, in order not to compromise the nasal valve system, is by following a 'high to low to high' approach (Fig. 2). This study was designed to deal with the following questions: does rhinoplasty affect nasal airflow? And, if so, which anatomical elements are responsible for these changes?

## Material and methods

Fifty-six patients were selected for this study and were subdivided into two groups: the first group consisted of 50 primary rhinoplasty cases (17 males, 33 females, mean age 24 years), and the second group of six secondary cases (three males, four females, mean age 33 years). All participants were asked the following question:

- Compared to your ability to breath through your nose before the operation, is your breathing now better, worse, or the same?

The physical examination was particularly directed towards the nasal valve area, and a group of ten patients additionally underwent acoustic rhinometry. The following lesions were found in the group of secondary cases: step deformity, synechiae, pinched tip (from interruption of domes and/or suture of domes), upper lateral cartilage detachment, nasal valve collapse, septal deviation at the nasal valve area, vestibular scar tissue. Patients presented with one or more lesions. The surgical technique, performed under general anesthesia, was as follows: inter-cartilaginous and transfixion incisions; removal of the hump by means of Fomon's scissors for cartilage and a 14–16-mm osteotome for the bony hump; medial osteotomies to mobilize the nasal bones; lateral and superior micro-osteotomies via a percutaneous approach with a 2-mm osteotome following a 'high to low to high' line;[10,13-15] delivery technique for tip plasty. If necessary, in secondary cases, the surgical technique should include outfracture of a narrow piriform aperture.[16] At the end of the operation, the nose was packed with vaseline gauze (primary cases) and with Stip® and/or Lyofoam® (secondary cases), to provide more efficient packing. A metal splint (Audio®) was used to hold the fractured bones. Postoperative follow-up was scheduled for 15 days, and one and three months.

## Results

With regard to the primary cases, the patients replied to the questionnaire as follows:

- 43 patients (86%) same
- 4 patients (8%) better
- 3 patients (6%) worse

Acoustic rhinometry showed reduced airflow in one case (2%) (not from the 'worse' group, not statistically significant). On rhinoscopic examination, all patients were negative for nasal stenosis, although a scar could usually be seen at the level of the intercartilaginous incisions, apparently being displaced slightly toward the septum at the caudal border of the upper lateral cartilages.

With regard to the secondary cases, six of the seven patients noted improvement in breathing, according to the questionnaire and the physical examination, and one case noted no change, due to vestibular scar tissue.

## Discussion

Although surgeons generally strive to avoid reducing nasal airflow during aesthetic rhinoplasty, there is still no definitive means of follow-up and assessment, especially in the long-term following these procedures. Studies often have mixed results, based on functional and cosmetic cases, different methods of nasal flow evaluation, *i.e.*, acoustic rhinometry and anterior active rhinomanometry, different surgical techniques, etc. Breathing modifications are often offset by the patient's subjective satisfaction with the aesthetic outcome, making it difficult to compare results.

The correct approach to this problem must take into account the nasal valve, which is undoubtedly the most critical anatomical structure in the procedure. It has the smallest cross-sectional area of the entire respiratory tract and consequently produces the greatest resistance to airflow. The nasal valve consists of, and is essentially limited by, the caudal end of the upper lateral cartilages and the corresponding septum and nasal floor. This is why, during a lateral osteotomy, medial displacement of the nasal bones causes the inner tissue to approach the septum, thus reducing this critical area. Some authors stress the importance of a high lateral osteotomy,[7,10,12-14] while others attach less importance to this approach, since they do not consider it to be critical.[1-6] Based on our results (primary cases), we inferred that a pure rhinoplastic procedure does not reduce subjective airflow in the majority of patients (47/50). The three cases of referred nasal obstruction could have been due to pre-existing anatomical conditions or postoperative vasomotor reactions. As far as the secondary cases are concerned, nasal airflow improved in six of the seven patients, showing that, even after two rhinoplastic procedures, the simple re-establishment of the correct nasal anatomy leads to the recovery of normal breathing. The patient who reported no return of function confirms our opinion that vestibular scarring is one of the most difficult iatrogenic lesions to repair.

The surgical technique described in this article would appear to be safe for the purpose it was used, but we must emphasize the importance of recognizing

any pre-existing anatomical or pathological conditions well ahead of the procedure. We feel that the key to safe and intact nasal breathing in patients undergoing rhinoplastic procedure is the careful application of the correct surgical technique. Our technique primarily stems from two warnings: firstly, do not start lateral osteotomy too low;[7] secondly, to avoid excessive medical displacement of the nasal bones, outfracture the nose after infracture.[16] Surgical details also include: minimal incisions; minimal elevation of the soft tissue; preservation of the lateral portion of the upper and lower cartilage; suture of all incisions; avoid pinching of the splint. The present article would seem to confirm the importance of carrying out rhinoplasty correctly. Our current knowledge on rhinoplastic techniques is adequate for preventing the impairment of nasal function.

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# NOVEL SURGICAL TECHNIQUES FOR TONGUE BASE OBSTRUCTION ASSOCIATED WITH SLEEP APNEA

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## Introduction

The success of the surgical management of obstructive sleep apnea (OSA) has relied heavily on the recognition that patients with moderate to severe sleep apnea usually have sleep-related collapse of multiple segments of the upper airway. These segments have been loosely categorized as retropalatal and retrolingual,[1] although some authors have also begun to quantify the degree of lateral pharyngeal wall collapse (from lateral to medial).[2]

Multilevel pharyngeal surgery is typically required to overcome these multiple levels of pharyngeal airway collapse;[3] and Fujita *et al.*[1] have achieved good outcomes with soft tissue modification, and Riley *et al.*[4] have pioneered utilization of skeletal techniques to enlarge the upper airway.

A new technique has recently been introduced that improves the nocturnal retrolingual airway without the morbidity of a midline glossectomy, nor the potential risks of a mandibular osteotomy with genioglossal advancement.[5] The tongue suspension procedure represents one of several new minimally invasive techniques that may prove to be valuable in patients with obstructive sleep apnea syndrome.

## Material and methods

A retrospective analysis was undertaken of data which were prospectively gathered on patients evaluated by the University Otolaryngology Service at Stanford University between March, 1998 and June, 1999, for the presence of sleep-disordered breathing (SDB). All patients underwent a complete head and neck evaluation (including fiberoptic endoscopy and a Müller maneuver[6]), and

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polysomnographic testing. Demographic data that were collected included age, gender, severity of SDB (apnea/hypopnea index (AHI) and lowest recorded oxygen saturation (LSAT)), degree of sleepiness as determined by the Epworth sleepiness scale (EPW), body mass index (BMI), type of surgery and surgical outcomes. Patients in whom evidence of both retropalatal and retrolingual obstruction was manifested, were offered multilevel pharyngeal surgery, consisting of a palatopharyngoplasty with either mandibular osteotomy with genioglossal advancement or tongue suspension (with the Repose device).

Nineteen consecutive patients who underwent multilevel pharyngeal surgery with tongue suspension using the Repose device form the cohort evaluated in this study. All patients underwent a simultaneous uvulopalatopharyngoplasty.

*Surgical techniques*

The palatopharyngoplasty procedure utilized has been described previously.[3] The tongue suspension procedure is performed through a floor-of-mouth incision using the Repose device as described originally by DeRowe *et al.*[5] A small (4 mm) screw to which a heavy (#1) prolene suture is attached is secured to the lingual surface of the anterior mandible. The suture is passed submucosally around the posterior tongue, and tied at the front in the floor of the mouth. The incision is closed with absorbable sutures.

## Results

There were 17 males and two females, with a mean (±SD) age of 47.9 ± 13.2 years. The mean (±SD) preoperative AHI was 39.8, with an apnea index (AI) of 14.3. The mean EPW score fell from 11 to 7. The BMI remained essentially unchanged (36.9-37.9). Anatomical and radiographic changes as a result of surgery are depicted in Figure 1.

Five of the 19 patients have had postoperative polysomnography. All these five patients (100%) met the standard criteria for surgical response (50% reduction in the AHI and a postoperative AHI <20, or 50% reduction in the AI and a postoperative AI<10), while four of the five (80%) met the stricter criteria that only acknowledged the improvement in the AHI. Of these five patients, the AHI improved from 30.6 to 13.6, while the AI improved from 7.1 to 0.8.

*Complications*

Four patients suffered transient velopharyngeal insufficiency, and two patients complained of limited anterior excursion of the tongue. There were no serious, long-term complications.

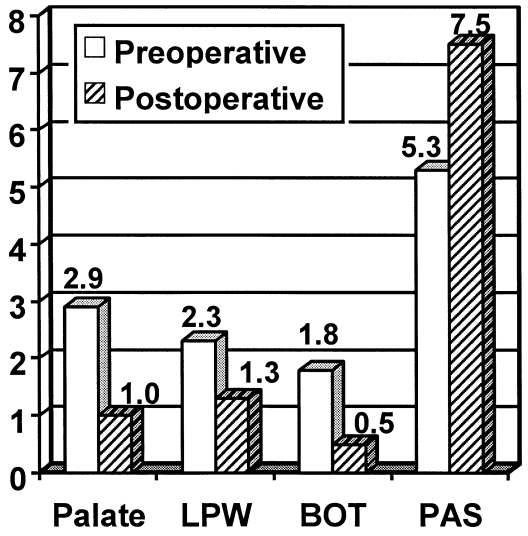


*Fig. 1.* Comparison of preoperative and postoperative values for both anatomical and radiographic measures of the upper airway in patients who underwent multilevel pharyngeal surgery (palatopharyngoplasty and tongue suspension with the Repose device). Note the moderate improvement in the palatal, lateral pharyngeal wall (LPW), and base of tongue (BOT) collapse seen on Müller maneuver examination, as well as mild improvement in the posterior airspace (PAS) seen on lateral cephalometric X-ray.

## Discussion

Moderate to severe obstructive sleep apnea is usually associated with multilevel pharyngeal collapse. Therefore, multilevel surgery is required to overcome the collapse at these segments. Both soft tissue[1] and skeletal framework[2] approaches to multilevel surgery have been advocated,[3,4] but each carries with it a significant degree of morbidity. Recently, DeRowe and coworkers[5] introduced a novel technique of tongue suspension, designed to improve the retrolingual airway.

We have achieved a moderate degree of success by combining the tongue suspension procedure with palatopharyngoplasty in a small number of patients. The anatomical improvement (as determined by the Müller maneuver) is similar to that obtained after mandibular osteotomy with tongue advancement. The radiographic improvement in the posterior airspace is modest, as might be predicted, since the goal is to stabilize and support the posterior tongue, rather than to advance it. The encouraging polysomnographic results seen so far in this small group of non-randomized patients will need to be confirmed in a larger cohort, and long-term durability of the anatomical improvement will need to be demonstrated. However, this would appear to be a promising new technique for the surgical management of obstructive sleep apnea.

## Conclusions

The tongue suspension procedure represents a minimally invasive technique for improving the nocturnal retrolingual airway in patients with obstructive sleep apnea. It is easily performed by the average otolaryngologist, thereby distinguishing it from other techniques designed to address tongue-base obstruction.

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# MODIFIED UVULOPALATOPLASTY

## Retrospective survey of patient satisfaction*

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*Introduction:* Snoring is a distressing symptom for the patient and his/her partner. It can also be associated with obstructive sleep apnea. Surgical management of snoring is aimed at reducing the soft palate by removing redundant tissue when the problem lies at the soft palate level. Different techniques have been described to create stiffening of the palate to reduce snoring, but long-term outcome and morbidity due to pain in the immediate postoperative period remain a major concern.
*Method:* The authors propose a new technique with the aim of improving the outcome of surgery and reducing postoperative pain. The procedure was carried out under general anesthesia, using either a laser or diathermy to excise the uvula and a triangular wedge (inverted 'V' shape) from the soft palate. The cut surface of the soft palate was sutured together with soft gut. Five ml of 0.05% marcaine was injected around the operated area. A retrospective survey was carried out via a questionnaire which was filled in by patients who had undergone surgery in the previous six months.
*Results:* Thirty patients filled in the questionnaire: in 28 of whom (93%), snoring had disappeared completely or was reduced to such a level that it did not disturb either them or their partners. Postoperative pain was reported for up to 14 days: ten patients (33.33%) reported pain lasting for 14 days, the remainder for less than ten days. Pain was well controlled with a combination of paracetamol and codeine. Fourteen patients (46.6%) had postoperative nasal regurgitation, which resolved within a few days. Three patients (10%) noted an alteration in speech in the immediate postoperative period, but this was of short duration. Fifteen patients had been sleeping in a separate room from their partners before the operation, which number dropped to just four (13.3%) after the operation. Twenty-one (70%) patients responded positively regarding recommending this operation to friends or family members, five (16.6%) were uncertain whether they would recommend it, and four patients (14.4%) declined to recommend it.
*Conclusions:* The six-month postoperative results show that this new technique is successful in reducing snoring, and that it is also less painful. These results are encouraging and are more long-lasting than other methods.

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# SNORING AND OBSTRUCTIVE SLEEP APNEA SYNDROME TREATED BY COST-EFFECTIVE, LOW PAIN, PHARYNGEAL VOLUME REDUCTION UNDER LOCAL ANESTHESIA

## Coblation-assisted upper-airway procedures*

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A variety of uvulopalatopharyngoplasty (UPPP) procedures has been developed for widening the pharynx by means of removing or reducing the pharyngeal soft tissue volume in order to treat snoring and sleep apnea. Different success rates (30-80%) have been reported in the literature.

A fairly new series of low-frequency, bipolar radiowave instruments (Coblation), which combines effective low pain volumetric tissue reduction and excision possibilities, has recently been introduced.

One hundred otherwise healthy patients, suffering from snoring and moderate sleep apnea (AHI <30), and with their main level of obstruction (> 2/3) in the upper pharyngeal region, were selected. This was done by performing a complete ENT examination, including endoscopy and all-night monitoring, with recordings of pharyngeal and mid-esophageal pressure fluctuations (apnea graph), which also provided the opportunity to diagnose the presence of upper airway resistance syndrome (UARS).

The entire group was treated by Coblation-assisted upper-airway procedures (CAUP) for problems in the upper pharyngeal region. These include palatal incision and upward channelling, as well as partial uvulectomy and channelling. If necessary, palatal arch, tonsil pillar and tonsil channelling were performed.

All the patients were controlled after six and 12 months, with an average number of treatments of approximately 1.3. The one-year follow-up results showed the classification and treatment to be extremely satisfactory, with proper results for more than 90 of 100 patients. Almost no unwanted side-effects were seen. Further results will be presented shortly.

*Conclusions:* The classification of snorers and obstructive sleep apnea syndrome patients, accompanied by step-wise treatment with bipolar low-frequency radiowave equipment (CAUP) as an out-patient procedure under local anesthesia, seems to give acceptable results. As seen on long-term follow-up, this is a complete and logical method for the step-by-step treatment of snoring and mild obstructive sleep apnea. The method will be described in detail and the results presented.

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# IMPROVEMENT OF SLEEP-BREATHING DISTURBANCES POST REPOSE TONGUE STABILIZATION PROCEDURES*

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Tongue stabilization using the Repose™ bone-to-soft-tissue anchor is a new minimally invasive technique that prevents tongue base collapse in patients with sleep-breathing disturbances (SBD). The authors present the results of 39 patients (34 male and five female), as measured by polysomnography, for a mean follow-up of 8.5 months (range: 3-21 months).

Thirty-seven of the patients were diagnosed with obstructive sleep apnea (OSA), while the remaining patients were classified as snorers. Four patients had been treated previously for their SBD with various (either conventional or surgical) methods. Three of the patients had been treated conservatively with bi-level or continuous positive airway pressure (BiPAP or CPAP) treatment, but had not tolerated these treatments well. Two patients had been treated surgically by uvulopharyngoplatoplasty (UPPP) and/or septoplasty (one case).

The average preoperative RDI of the patients was 48.3 (range: 9.9-100) events per hour. Their overall lowest oxygen saturation percentage was 79.4% (range: 53-92%).

The majority of the patients underwent other procedures in addition to the tongue stabilization. Thirty-five patients underwent UPPP, 21 had their inferior turbinates reduced, 11 had septoplasty, and eight had tonsillectomy. The average postoperative RDI of the patients was 13.3 events per hour, (> 72% reduction versus preoperative RDI). The average lowest oxygen saturation percentage improved by 9% to 88.4% (from an average of 79.4%) as a result of the procedures. Subjectively, 37 of the 39 patients who were interviewed postoperatively mentioned an improvement in the status of their SBD. Two patients reported that their condition had not improved. Two patients required further surgical intervention, such as maxillomandibular or genioglossal advancement. Two patients could use their positive airway pressure devices successfully, thanks to the procedures. In one patient, recurrence to the preoperative RDI level was observed.

Although tongue stabilization was performed as part of a multistage procedure in most patients, the results appeared better than expected with only one level of treatment.

Repose tongue stabilization can be regarded as a viable technique for the improvement of SBD, especially in patients with obstructive sleep apnea with multilevel sites of airway collapse.

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# LONG-TERM FOLLOW-UP OF PATIENTS UNDERGOING PALATAL SOMNOPLASTY*

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*Aim:* To assess the effectiveness of palatal somnoplasty in the treatment of snoring.
*Method:* A study was undertaken using a simple anonymous questionnaire sent to all patients who had undergone palatal surgery by the senior author. All patients within the study were chronic habitual snorers who had initially been referred for snoring problems. All patients had undergone preoperative polysomnography, to exclude sleep apnea and sleep naso-endoscopy, in order to rule out tongue-base collapse as a cause for their snoring. No patient underwent palatal somnoplasty with a body mass index in excess of 27. All patients were asked to complete a questionnaire. Information was requested on time since operation. A visual analogue scale (VAS) was used to document preoperative from postoperative snoring from the patient and bed partner. Postoperative pain was also assessed using VAS.
*Results:* Fifty-nine questionnaires were sent to patients, 36 of which (61%) were returned. The mean time since operation was 17.5 months (range, 3-39 months). The median preoperative snoring score was 9 on VAS; following the procedure this score was reduced to 7. This reduction included all patients in the study even if there had been no improvement in the snoring. Twenty-one patients (61%) reported an improvement in their snoring, and just eight (22%) reported a > 50% reduction. This figure is generally quoted in studies as a level at which the operation can be regarded as being successful. Postoperative pain was also assessed using VAS: the median score was 0 (range, 0-8).
*Conclusions:* Short-term results of palatal somnoplasty have suggested a high (83%) success rate in treating snoring within six weeks of surgery. However, our longer-term results suggest that the percentage of patients with a successful result over a longer term reduces to approximately 22%. However, despite these low figures, 50% of the patients in our study remarked that they would undergo further palatal somnoplasty, and only 22% would not have further surgery. Palatal somnoplasty is a procedure with a low morbidity, is less disfiguring than other forms of snoring surgery, and can be repeated. Therefore, it may still have a role to play in managing this condition.

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# NONSURGICAL THERAPIES

# FUNCTIONAL ELECTRICAL STIMULATION OF THE NERVUS HYPOGLOSSUS FOR OBSTRUCTIVE SLEEP APNEA SYNDROME TREATMENT

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## Introduction

Upper airway occlusion in patients with sleep-disordered breathing has been attributed to a collapse of the pharyngeal airway. Among the different mechanisms involved, a decline in pharyngeal (genioglossus) muscle activity has been implicated.[1]

Previous studies in human subjects have shown that a significant improvement in maximal inspiratory airflow can be obtained by selectively stimulating the genioglossus muscle during sleep, using fine wire electrodes.[2] Based on these findings and data from animal studies, a system for functional electrical stimulation of the hypoglossal nerve (NXII) has been developed: the Inspire I™ system (Medtronic Inc, Minneapolis, MN). This system consists of an implantable pulse generator, a respiratory pressure sensor, a half-cuff stimulation lead, and a programming system. Stimulation occurs early during inspiration and is triggered by intrathoracic pressure changes during the respiratory cycle. A patient-programmer allows fine tuning of stimulation parameters by the physician during postoperative polysomnographies.

## Results

Worldwide, eight patients were included in a feasibility study to investigate the effect of NXII stimulation on obstructive sleep apnea. Three of these were

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*Table 1.* Patient characteristics at baseline, and RDIs before implantation, six months after implantation and stimulation parameters

| *Case* | *Age (years)* | *BMI ($kg/m^2$)* | *RDIpre (n/hour)* | *RDIpost (n/hour)* | *Amplitude (Volt)* | *Frequency (Hz)* | *Pulse width (μsec)* |
|---|---|---|---|---|---|---|---|
| 1 | 57 | 31.4 | 68.1 | 16.6 | 2.2 | 40 | 91 |
| 2 | 54 | 34.4 | 29.3 | 21.5 | 2.2 | 33 | 117 |
| 3 | 55 | 25.8 | 56.7 | 17.1 | 3.0 | 40 | 91 |

BMI: body mass index

recruited from the ENT Department of the Antwerp University Hospital, Belgium. All were patients with severe obstructive sleep apnea (OSA) treated by continuous positive airway pressure (CPAP), but who were seeking an alternative mode of treatment. Baseline characteristics and respiratory disturbance index (RDI), stimulation parameters, and RDI at six months after implantation, are shown in Table 1. Follow-up data are reported as 'intention to treat'.

The system is well tolerated by the patients and the reported use of the stimulator is good. Until now, no stimulation-related side-effects have been noted. In patient No. 3, the system failed because of problems with the half-cuff electrode. The system was removed at the patient's request and he is again using CPAP.

## Discussion

A marked improvement in sleep-disordered breathing could be demonstrated during NXII stimulation using the Inspire I™ system. Moreover, apnea and hypopnea could be prevented without patients being aroused from sleep. The data demonstrate that the improvement in obstructive apnea during hypoglossal stimulation can be attributed to recruitment of the genioglossus muscle and the concomitant reduction in upper airway collapsibility, and not to arousal from sleep.

One parameter for defining upper airway collapsibility is the critical closing pressure ($P_{crit}$). Previous studies have demonstrated that hypoglossal nerve (HGN) stimulation results in a decrease of $P_{crit}$ of approximately 5 cm $H_2O$.[3] With the knowledge that $P_{crit}$ must fall below approximately –4 cm $H_2O$ in order to relieve upper airway obstruction, and knowing the amount of reduction in $P_{crit}$ to be expected during stimulation, it might be possible to predict which patients are more likely to have their sleep-disordered breathing improved during stimulation, on the basis of their baseline $P_{crit}$ value[4].

The patients implanted at our center were selected on the basis of having predominantly tongue base obstruction (documented by intraluminal pressure measurements during sleep).[4] HGN stimulation results in tongue protrusion, which may account for the improvement in sleep-disordered breathing. Yet, although the patients implanted at other participating centers were not included on the basis of the

site of upper airway obstruction, a similar improvement in obstructive apnea was found. Moreover, in a feline upper airway preparation, upper airway collapsibility decreased significantly during NXII stimulation and, in these animals, the site of obstruction is located at the rim of the soft palate.[5] Further studies are thus required to investigate whether the site of upper airway obstruction should be taken into account when selecting patients for this type of treatment.

Another feature likely to affect treatment efficacy is the presence of concomitant central sleep apnea. Since stimulation is triggered by respiration, as detected by the transsternal pressure sensor, it can be anticipated that the system will fail to do so in the absence of respiratory movement (central apnea). Although upper airway occlusion has been demonstrated during central apneas, alterations in ventilatory drive are the primary mechanism in this disorder.

Optimization of the stimulation parameters requires fine tuning, and regular visits are necessary to achieve these goals. Therefore, good cooperation by the patients, and their understanding of the treatment, are prerequisites for therapeutic success.

## Conclusions

Functional electrical stimulation of the HGN by the Inspire I™ system results in a substantial improvement of sleep-disordered breathing in carefully selected patients. Our findings suggest that NXII stimulation may be considered as an alternative to CPAP treatment in patients with dominantly OSA. Further studies are necessary to define patient selection criteria, based on baseline measurements of upper airway collapsibility and site of upper airway obstruction.

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# CONSIDERATIONS ON THE USE OF MECHANICAL NASAL DILATOR DEVICES

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## Introduction

In normal subjects, nasal airflow resistance is responsible for about half the total work involved in breathing,[1] so the nasal passage is the main source of flow resistance in the respiratory tract. The nasal valve area in particular is the narrowest portion of the nasal fossa and, for that reason, it is the site of the most resistance[2]. The nasal valve area is a triangular, slit-like opening, located in the anterior portion of each nasal fossa, between the caudal ends of the upper lateral cartilage (laterally) and septum (medially). Another critically narrow site is the nasal passage between the free edges of the inferior turbinate and the nasal septum, so that the nasal valve and head of the inferior turbinate can be considered anatomical 'serial' structures in determining anterior nasal resistance.

The anterior nasal portion is a frequent site of pathology causing nasal obstruction. The nasal valve and surrounding area can be compromised by numerous anatomical and physiological changes. Pathological conditions at these levels are strongly influenced by the presence of anatomical structures, both skeletal and mucosal. As far as the alterations that concern the osteo-cartilaginous frame of the nose are concerned, we must take into account: anterior septal deviation, collapsed ala nasi mainly due to senile atrophic changes or Bell's palsy, post-rhinoplasty status, and scarring from burns or trauma. Pathologies that can affect the mucosal and submucosal layers consist of increasing volume of the inferior turbinates due to the common cold, allergic, pseudo-allergic and pharmacological rhinitis, and rhinitis during pregnancy.

There are essentially three types of therapeutic options in these cases, as follows: medical, surgical, and prosthetic. Local pharmacological treatment, such as vasoconstrictors, acts by decreasing nasal mucosal swelling, thereby reducing the volume of the turbinates; their effectiveness in lessening nasal resistance has been widely reported in the literature,[3,4] as their potential risks

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due to chronic or excessive use. Surgical treatment can consist of correcting the deviating nasal septum or the nasal valve itself, remodeling and widening of the ala nasi, and reducing the volume of the inferior turbinates. Prosthetic treatment, such as mechanical nasal dilators, act by expanding the ala nasi and thereby increasing the cross-section at the level of the nasal valve area.

Many types of nasal dilators have been proposed since 1905, essentially for supporting collapsed ala nasi in order to reduce the nasal obstruction and improve the cosmetic appearance.[5] There has been renewed interest in these mechanical devices; it has been shown that mechanical dilation of the nasal airways during sleep can decrease the frequency and severity of obstructed breathing events in obstructive sleep apnea syndrome (OSAS) patients.[6,7]

A very diffuse type of internal dilator, the Nozovent, is made of a soft elastic plastic strip which is introduced into the nostrils after the end tabs have been pressed together by the fingers.[8] The Breathe With Eez Mechanical Therapeutic Nasal Dilator is made of biocompatible 304 stainless steel alloy wire, formed as a looped spring, flexible, collapsible and self-expanding. It conforms to any size and shape of nasal vestibule: by gently exerting outward pressure in all directions, it dilates the nasal valve and deflects the anterior portion of the nasal septum.[9]

## Clinical experience

One of the devices we have considered, an endonasal type in premodeled rigid plastic (model Beldormir), available in three sizes, is shown in Figure 1; the correct way to fit this device in a patient with valvular nasal obstruction is shown on the right.

The most well-known external dilator (Breathe Right, 3M) frequently used during sport and also available in various sizes, is applied on the nasal pyramid by an adhesive strip, positioned on the anterior part of the nasal pyramid, above the ‘weak triangle’ between the inferior lateral margin of the triangular cartilage and the lateral superior margin of the alar cartilage.

Our clinical experience mainly concerns patients with a wide range of pathologies: pseudo-allergic rhinitis, rhinitis during pregnancy, anterior septal deviation, collapsed ala nasi due to senile atrophic alterations, as well as deformity of the anterior part of the nasal pyramid in patients with severe facial palsy after surgery for cerebellopontine angle tumors.

In Figure 2, the rhinomanometric tracing of a patient with anterior septal deviation and obstructed right nasal fossa shows reduced right nasal resistance after an internal dilator has been inserted.

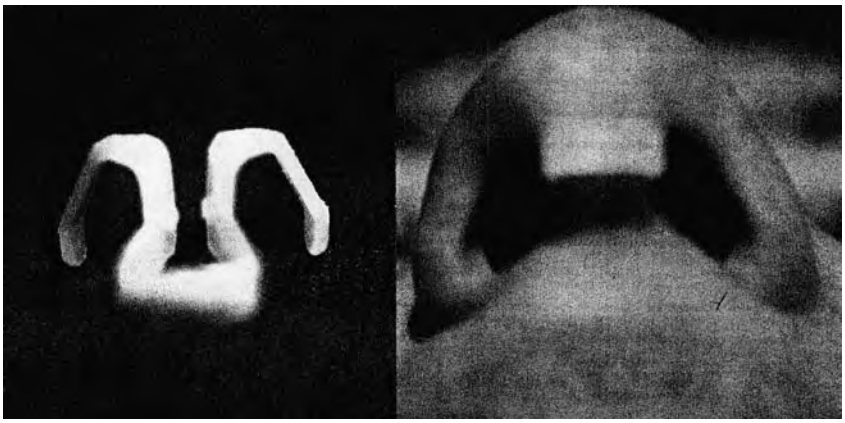

*Fig. 1.* Endonasal mechanical dilator (model Beldormir). The correct way to fit this device is shown on the right.

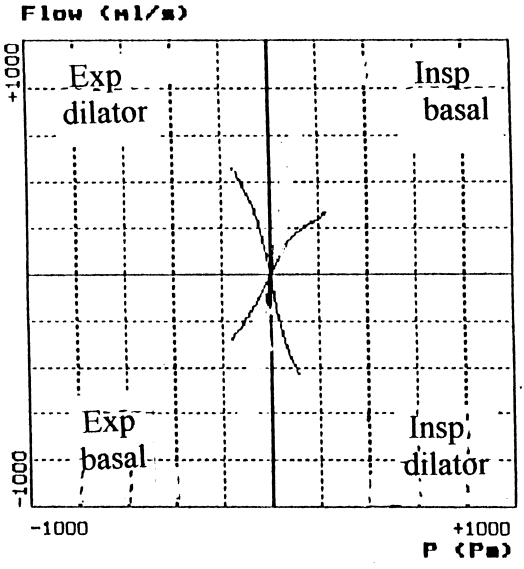


*Fig. 2.* Rhinomanometric tracing of a patient with anterior septal deviation. Reduced nasal resistance can be seen after insertion of an endonasal mechanical dilator.

## Discussion

After our experience with these two types of dilator for the above-mentioned pathological conditions, a few observations can be made. Above all, we can confirm that the degree of nasal obstruction is reduced, both subjectively and on the grounds of the results of objective testing using both types of device. In fact, both dilators act on the same anatomo-functional structure, one by lifting up externally, the other by pushing from the inside, even though the external

device proved to be less efficient on evaluation by objective testing (rhinomanometry). However, the patient must be carefully taught how to place each type of dilator correctly, since the actual effect of such a device strongly depends on this.

The relative advantages and disadvantages of the two models are as follows:

– owing to the rigidity of its structure, the internal device guarantees a relatively constant degree of dilation of the valvular area, also due to the variations in mechanical resistance offered by the lateral walls of the nose. Furthermore, it can be used more than once and is therefore more economical. The most evident disadvantage is a certain degree of discomfort reported by almost all patients. In fact, in our opinion, the rigid type of material makes it inappropriate for long-term use, due to cases of endonasal scratching and vestibulitis;
– the use of the external device seems to be more acceptable to the patient, even though it is less efficient as a dilator. The main disadvantages are its cost (can only be used once) and some patients noted slight irritation of the skin of the nasal dorsum.

In conclusion, in our experience, the indications for the use of mechanical nasal dilators, particularly in relation to surgical or pharmacological options, are:

– pathological conditions causing transitory functional nasal obstruction, particularly when drug treatment is not to be recommended (*e.g.*, during pregnancy) or has not proved to be helpful (pseudo-allergic rhinitis);
– situations in which surgery is definitely or preferably not an option (*e.g.*, in the elderly), or when it has been refused (*e.g.*, in cases of facial palsy).

As far as the use of nasal dilators in the treatment of snoring and OSAS is concerned, they would appear to be useful in selected cases in which an anterior nasal obstruction has been identified as the main etiological factor.

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# ORAL APPLIANCES FOR THE TREATMENT OF SNORING AND OBSTRUCTIVE SLEEP APNEA

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## Introduction

Due to its well-documented effectiveness and the lack of relevant side-effects, application of continuous positive airway pressure (CPAP) via a nasal mask is currently the standard therapy for obstructive sleep apnea syndrome (OSAS).[1,2] It provides symptomatic relief and normalizes respiration, sleep structure, and vigilance. Nevertheless, the inconvenience of wearing a nasal mask and using the pressure generator every night as well as psychological and other reasons, make CPAP therapy unacceptable for many patients. Compliance with this treatment is therefore less than ideal.[3,4]

Among the non-surgical alternatives for the treatment of OSAS, oral appliances have gained increasing popularity.[5-7] This is because they are easy to apply, handy, not dependent on electrical power, and thus particularly suitable for use during travel. Furthermore, the stigma of OSAS is less evident and psychologically less disturbing with an oral appliance, than with CPAP treatment.

In the following, we will discuss design and principles of action, effectiveness, side-effects of oral appliances for the treatment of OSAS and snoring. We will conclude with some practical recommendations for their application.

## Design and principles of action of oral appliances

### *Design*

Most of the multiple types of removable oral appliances that have been proposed for treatment of snoring and OSAS belong to one of the following three main types of devices:[6,7]

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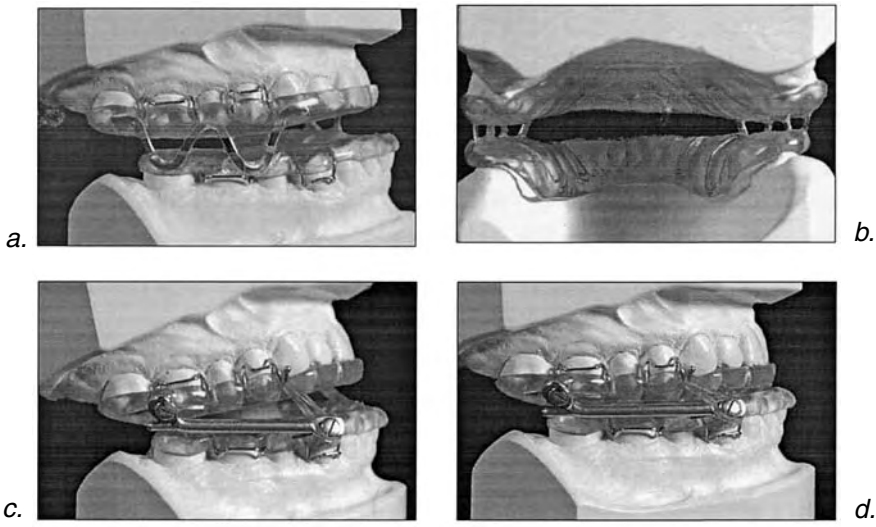



*Fig. 1.* The sleep-apnea-Monobloc *(a, b)* and Herbst appliances *(c, d)* are examples of mandibular advancement devices. They differ from each other in that the Monobloc consists of two pieces held firmly together by stainless steel wire, while the lateral telescopic rods that connect the two pieces of the Herbst appliance allow for some limited lateral, opening and protrusive motion of the mandible. The elastics prevent mouth opening during sleep. Both appliances are snapped onto the upper and lower teeth and are held in place by the fit of the pieces and metallic clasps. They provide full occlusal coverage. The posterior view *(b)* shows that the lower, buccal part of the device has an extension that distributes protrusive forces, not only to the teeth, but also to the alveolar process of the mandibular bone. The devices are made of methyl-methacrylate, a robust material that allows thickness to be reduced to a minimum in order not to encroach upon tongue space.

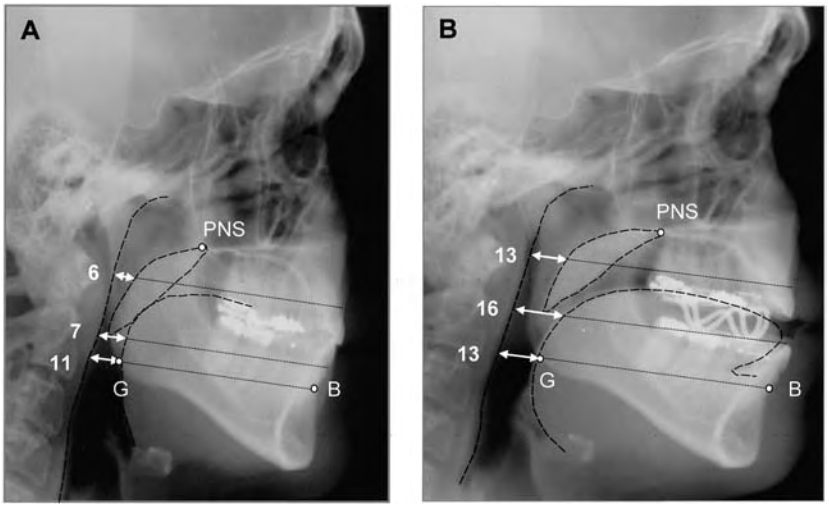
- *Mandibular advancement devices (MAD):* these devices are snapped onto the upper dental arch[8] or the upper and the lower dental arches.[9,10] They are designed to force the mandible into a protrusive (anterior) position, thereby increasing the upper airway lumen (Fig. 1a-d);
- *Tongue-retaining devices:* these devices are thought to increase upper airway size by exerting anterior traction on the tongue. The latter is contained within a plastic bulb and is held in this position by subatmospheric pressure;[11,12]
- *Palatal lifting devices:* these devices are inserted into the oral cavity and are held in place by being snapped onto the upper teeth. They have an extension that supports the soft palate to prevent its vibration during sleep. Experience with palatal lifting devices is very limited and they have not found widespread acceptance.[12]

Among the large variety of oral appliances, only MAD have been subjected to a more rigorous scientific evaluation in randomized controlled trials with regard to their effectiveness in the treatment of snoring and OSAS. Therefore, the following discussion is focused on this type of device.

*Principles of action of mandibular advancement devices*

The goal of MAD is to prevent upper airway collapse and vibration during sleep in order to eliminate apnea/hypopnea and snoring. As the name implies, this is achieved by protrusion of the mandible. It is a well-known clinical fact that the noisy obstructive breathing seen in some spontaneously breathing patients during anesthesia can be improved by pulling their mandible forward by external manual traction. A similar principle, *i.e.*, forward displacement of the mandible, and with it of the tongue and other soft tissue structures, is thought to be the primary mechanism by which MAD enlarge the upper airway lumen and prevent upper airway obstruction during sleep (Fig. 2). This has been substantiated recently by a randomized crossover trial comparing a mandibular advancement splint with an oral plate that did not advance the mandible (placebo).[13] Patients had much greater respiratory and sleep disturbances during the nights with the oral plate serving as a placebo than during the nights with the mandibular advancement splint in place.

In one study,[14] the cross-sectional area of the upper airway increased with the amount of mandibular protrusion in a non-linear fashion. Up to an amount of 50% of maximal mandibular protrusion, the increase in pharyngeal cross-sectional area was modest, but the latter increased to approximately one and a half to two times the value measured in the resting position when protrusion was further increased to the maximal possible protrusion. As documented by means of video-endoscopy in another investigation,[15] insertion of a MAD




*a.* *b.*

*Fig. 2.* Lateral cephalograms without *(a)* and with *(b)* a MAD in place reveal increases in upper airway diameter at various levels with the device. The superior, middle, and inferior airway spaces are marked with arrows, and the corresponding antero-posterior diameters are indicated in mm. PNS: posterior nasal spine; G: gonion; B: B point. The contours of the uvula and tongue are outlined with dashed lines. (Reproduced from Fritsch and Bloch[47], by courtesy of *Therapeutische Umschau*.)

(Klearway™) resulted in significant enlargement and changes in the configuration of the upper airway lumen at various levels. The increases in cross-sectional area of the velopharynx observed after insertion of the MAD were significantly correlated with decreases in the apnea/hypopnea index measured during sleep studies with the appliance in place. As measurements of the upper airway dimensions in the cited studies[14,15] were obtained during wakefulness, and, depending on the methods used, required special positioning and instrumentation, these results may not reflect the conditions during natural sleep in unrestrained patients. The dose-dependent effect of mandibular adavancement on nocturnal oxygenation was demonstrated in 37 sleep apnea patients each successively using one of three MAD with a protrusion of 2-, 4- and 6-mm, respectively.[16] Nocturnal pulse oximetry revealed that the percentages of patients with >50% reduction of oxygen saturation dip rate were 25%, 48%, and 65%, respectively, with these MAD in place, compared to a baseline study with no mandibular advancement. In four OSAS patients studied during polysomnography, stepwise increases in protrusion achieved by an adjustable MAD were associated with progressive improvements in the number of apneas and hypopneas during sleep.[17]

In summary, protrusion of the mandible seems to be the essential feature of MAD. The reduction of sleep-related upper airway obstruction using MAD seems to be mediated by enlargement of the lumen, and by improving the collapsibility of the pharyngeal walls, possibly by modulation of pharyngeal muscle tone and passive compliance.[16,18]

## Effectiveness and side-effects of mandibular advancement devices

Over the past few years, the accumulating experience in the treatment of OSAS and snoring by MAD has been reflected in a growing number of reported case series. In addition, several randomized, controlled studies, which are discussed below and summarized in Table 1, have provided scientific evidence for the effectiveness of this treatment modality.

### *Subjectively perceived beneficial effects*

In several controlled trials published to date,[8-10,13,19,23] (Table 1), MAD provided significant improvement of OSAS symptoms. In the reports that mentioned changes in Epworth sleepiness scale scores (a scale ranging from 0-24 points with increasing sleepiness, and a normal range extending up to 11 points),[24,25] mean reductions ranged from 4-6.2 points.[9,10,13,20,22] This effect clearly exceeds that achieved with placebo tablets[26] or with sub-therapeutic (sham) CPAP[1] (mean improvements by two points). In three studies, subjective sleepiness was not significantly improved by MAD (changes in Epworth scores of two points or less).[21,23]

The effect of MAD on subjectively perceived snoring was evaluated in five

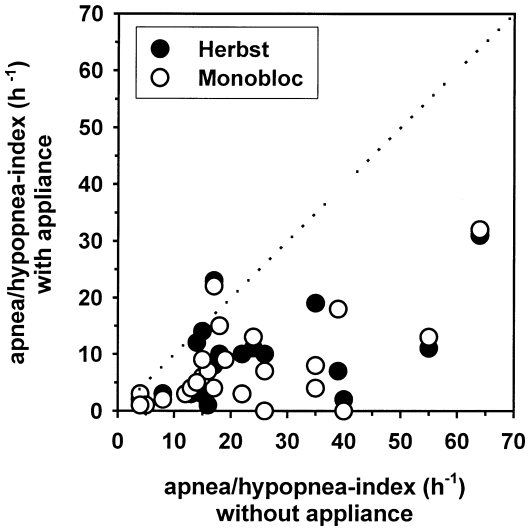



*Fig. 3.* The effect of two different types of MAD (sleep apnea Monobloc and Herbst appliances) on the apnea/hypopnea index was evaluated in 24 patients in a randomized controlled trial. With one exception, respiratory disturbances were improved during nights in which the Monobloc or Herbst appliances were applied, compared to a control night without treatment. (Reproduced from Bloch *et al.*[10] by courtesy of the *American Journal of Respiratory and Critical Care Medicine*.)

studies. In comparison to the untreated condition, MAD improved snoring.[9,10,13,20,27] In one study, the effect of MAD on snoring was less pronounced than that of CPAP.[9]

In four of five studies comparing MAD therapy with CPAP, patient satisfaction was greater with MAD than with CPAP.[8,9,19,21,22] In another study, patients were only included if they had refused or could not tolerate CPAP.[10]

*Effects on vigilance*

The effects of MAD on the objectively measured tendency of falling asleep in a dark room (maintenance of wakefulness test) were no different from those of CPAP in a randomized cross-over study.[21] Compared to a placebo appliance with no protrusion, MAD significantly improved mean sleep latency measured in the laboratory (multiple sleep latency test).[20]

*Effects on sleep and respiration*

The mean apnea/hypopnea index in all controlled studies[8-10,13,19-23,27] showed a significant decrease with MAD compared to the baseline condition without oral appliance (Table 1, Fig. 4). Furthermore, nocturnal oxygenation, reflected in the percentage of time spent at a saturation of SpO2 <90%, the minimal oxygen saturation, or the number of oxygen desaturations, was also improved

in some[10,13,19,20,23] but not all[8,9] studies. The amount of reduction in the apnea/hypopnea index, and oxygenation achieved with CPAP exceeded corresponding improvements with MAD.

Despite the favorable group effects, there were occasional patients in whom breathing disturbances with MAD in place were more pronounced than at baseline (Fig. 3).[9,10] It is worthy of note that some of these patients perceived a subjective benefit from their MAD, even in the absence of improvements in sleep-related breathing disturbances.

The effects of MAD on sleep structure seem to be less pronounced than those on respiration. In this regard, the results from various studies are not consistent. In five studies, the proportion of slow-wave sleep or REM sleep were slightly increased, or the number of arousals reduced, with a MAD in place.[10,13,19,20,22] In two other studies, neither the application of a MAD nor of CPAP was associated with changes in these variables commonly used to assess sleep quality.[8,9]

If a dichotomous analysis was performed with treatment success being defined as a reduction of the apnea/hypopnea index with MAD to 10 or less per hour, and improvement of symptoms, then the success rates of MAD therapy ranged from only 19%[9] to 88%[10] (mean value 57%, n=293).

In two controlled trials in habitual snorers without OSAS, snoring was found to be improved with MAD therapy.[28,29]

*Meta-analysis of the effects of MAD in obstructive sleep apnea therapy*

To date, the number of patients included in individual studies on MAD is still relatively small. Therefore, we performed a meta-analysis of randomized, controlled studies published up to June 2003, which assessed the effects of MAD on subjective sleepiness, and sleep-related breathing disturbances. References were retrieved from MedLine™ using the keywords sleep apnea, therapy, oral appliances, and mandibular advancement devices. Additional references cited in the retrieved publications were also reviewed. Data from various studies were pooled, and the weighted mean effects on outcomes calculated. [30] These data are shown in Figure 4. Some authors [31,32] reported a favorable experience with titrateable appliances, *i.e.*, devices with a mechanism (for example, a screw) that allows for easy adjustment of the protrusion by the dentist or even by the patients themselves, without the need for a technician. A separate analysis of the effects of titrateable versus non-titrateable appliances revealed similar effectiveness (Fig. 4). In Figure 4 (upper panel), individual trials are arranged in descending order of apnea/hypopnea indices at baseline. This shows a correlation between the severity of sleep-related breathing disturbances at baseline and that during treatment with MAD. A similar correlation was found for subjective sleepiness (Fig. 4, lower panel).

Treatment failure was defined as an apnea/hypopnea index during MAD therapy of more than 10 per hour, and/or no improvement of symptoms. The

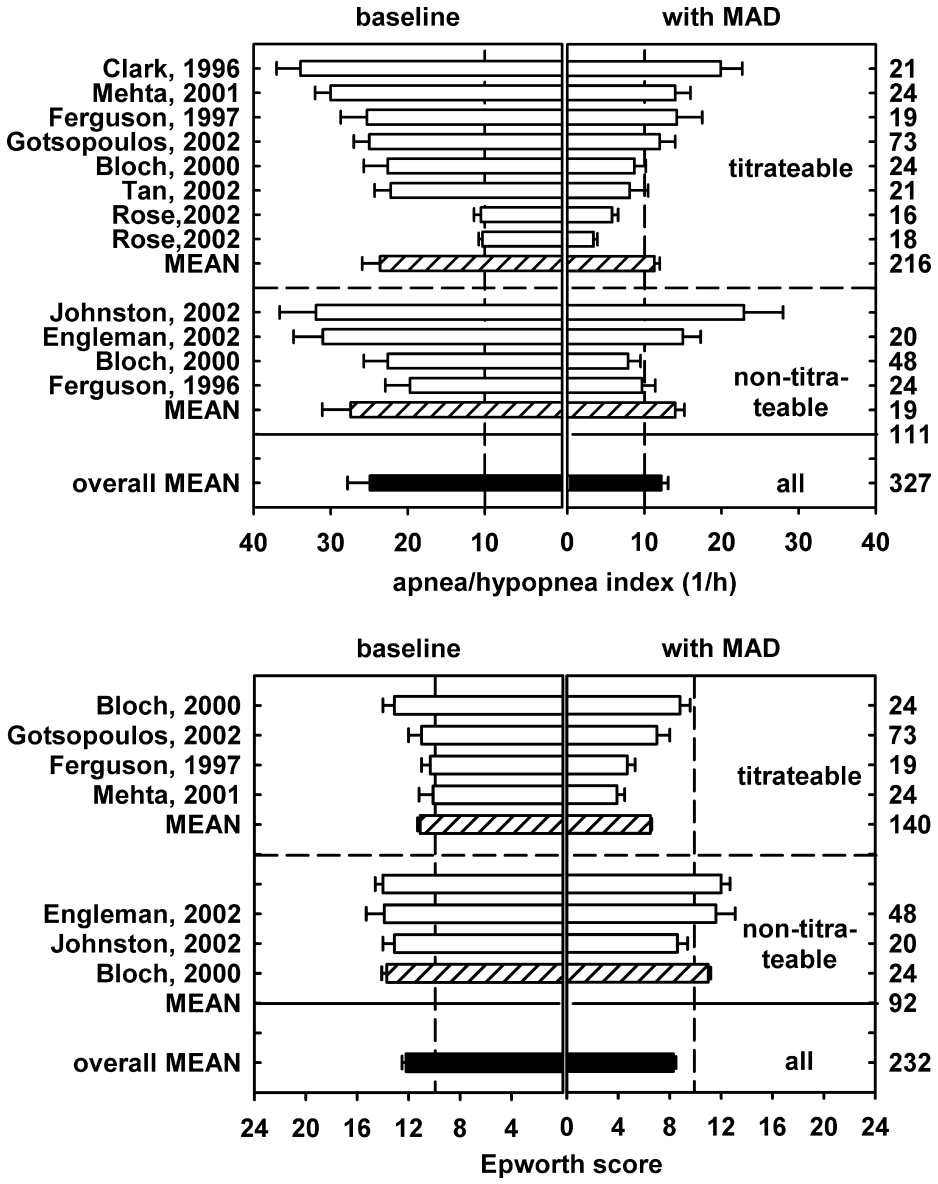



*Fig. 4*. Data from the randomized, controlled trials on the effects of MAD on sleep disordered breathing (upper panel) and subjective sleep propensity (lower panel) are summarized (see also Table 1). White columns with error bars represent means and SE from individual trials at baseline, and during MAD therapy; hatched columns represent weighted means from trials with titrateable and non-titrateable MAD; and black columns represent overall means. Trials are arranged in descending order of baseline apnea/hypopnea index and Epworth sleepiness scale scores, respectively. The first author and year of publication are indicated on the left y-axis, the corresponding number of patients on the right y-axis. Dashed vertical lines show an apnea/hypopnea index of 10/hour (upper panel), and an Epworth score of 10 (lower panel).

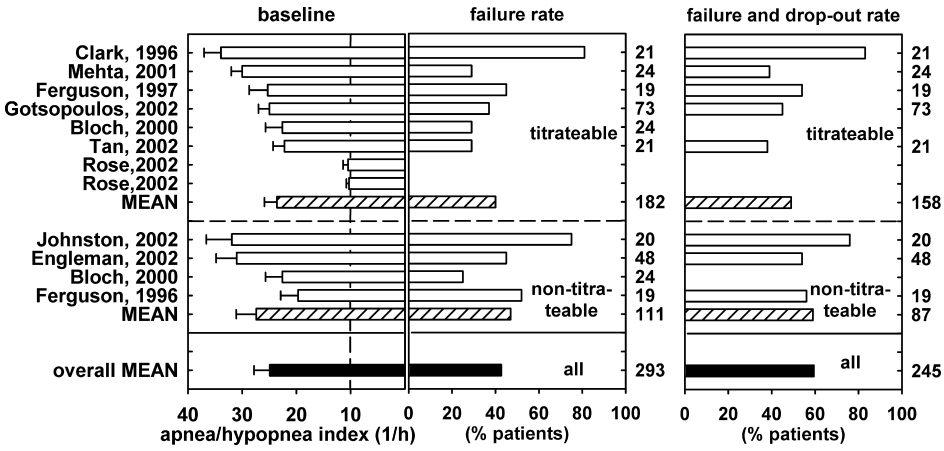



*Fig. 5.* The plot shows the failure rate (middle panel) and dropout rate (right panel) for the randomized, controlled trials listed in Table 1 and represented in Figure 4. Failure was defined as an apnea/hypopnea index of >10/hour with MAD and/or no improvement in symptoms. Dropouts are defined as patients who discontinued the protocol or were lost to follow-up. White columns with error bars (SE) represent mean apnea/hypopnea indices at baseline from individual trials; hatched columns represent weighted mean percentages of patients with treatment failure (middle panel), and combined percentages of failure and dropout (right panel) from trials with titrateable and non-titrateable MAD, respectively; black columns represent overall means. Trials are arranged in descending order of baseline apnea/hypopnea indices. The first author and year of publication are indicated on the left y-axis, the corresponding number of patients on the right y-axis. No columns are shown for papers in which relevant information could not be extracted.

analysis revealed an average failure rate of 43% in a total of 293 patients (Fig. 5). Since several studies were not analyzed on an intention-to-treat basis, a bias might have occurred, due to a significant proportion of patients being lost to follow-up. The combined dropout and failure rates were 53 % on average (Fig. 5).

*Side-effects*

Subjective side-effects during MAD therapy are common but usually of minor intensity and lasting only for a few minutes after removal of the MAD in the morning. The most common complaints include sore teeth and jaw muscles, and excessive salivation (Fig. 6).[8-10,23,32-34] These symptoms tend to improve over a few months during treatment.

Repeated measurements of dental geometry and occlusion over the course of long-term therapy (12-30 months) with MAD revealed a minor but statistically significant backward rotation of the tip of the upper incisors (decrease in the upper incisors to the maxillary plane angle), resulting in decreases in overjet and overbite.[34] Similar trends in orthodontic alterations, which were consistent


*Fig. 6.* Prevalence (number of patients affected) and intensity of side-effects from sleep apnea therapy with MAD over 12-30 months in 22 patients. Intensity was graded on a five-point Lickert scale, extending from 0 (not at all) to 5 (always, strongly disturbing). The vertical lines and boxes represent medians and quartiles, the whiskers the fifth and 95th percentiles, respectively.[34] Side-effects are common during treatment with MAP. However, the intensity is usually low, and the symptoms disappear after a few minutes when the appliance is removed in the morning.

with the expected consequences of forces acting on the upper and lower dental arches during protrusion of the mandible, were noted in various studies.[34-38] These observations indicate that close follow-up during long-term therapy with MAD is advisable in order to detect potentially relevant orthodontic changes in time.

*Adherence to treatment*

To date, objective data on adherence to treatment with oral appliance therapy are scant.[31] According to data derived from questionnaires in two studies,[8,9] patients used their MAD after four months of intended treatment in 76 and 95%, respectively. Corresponding data for CPAP therapy in these randomized cross-over trials revealed a lower adherence of 62% and 70%, respectively.[8,9] After an average treatment duration of one year, 86% of patients reported continued use of their MAD.[32] Long-term use for three years or more was 51-70% in other studies.[39-42] Good to excellent treatment adherence (74%[35] and 92%,[34] respectively) was found in selected patients who could not tolerate or had refused CPAP and therefore received a MAD as second line therapy.

## Practical recommendations

### *Patient selection*

As CPAP is highly effective in eliminating obstructive apnea and has no relevant side-effects, it is still the treatment of first choice for the majority of OSAS patients. Therefore, in most patients with OSAS, we first propose a treatment trial with CPAP. Among the exceptions to this rule are patients with a clear indication to a particular surgical therapy, such as in significant adenoid and tonsillar hypertrophy. In OSAS patients who are not able or not willing to use CPAP treatment, a MAD is a valuable alternative. In simple snorers without OSAS, we consider MAD to be an appropriate first line therapy since these subjectively asymptomatic subjects are unlikely to accept the inconvenience of wearing a nasal mask every night. Some simple snorers and some OSAS patients on CPAP therapy may benefit from MAD that can be applied as needed in certain situations only; for example, during travel and during vacations when they have to share a room with other people. As in other symptomatic long-term therapy that requires application of a device, the motivation of a patient for the treatment is crucial to its success. Therefore, we carefully explain the examinations required, and the steps in the fabrication and adaptation of a MAD before initiation of treatment. We emphasize the need for regular follow-up examinations during long-term treatment. In addition, we discuss the financial aspects of MAD therapy, in particular in subjects with simple snoring, as treatment for this condition is usually not covered by health insurance. After such detailed information, some patients first prefer to try other measures to control their snoring or mild sleep apnea, for example, weight loss or positional training.

To date, predictors of successful MAD therapy have not been clearly identified. In a retrospective analysis Metha *et al*.[13] found a positive correlation among neck circumference, apnea/hypopnea index without MAD, and cephalometric measurements at baseline with the apnea/hypopnea index during treatment with MAD. Another study[44] reported a positive correlation between the decrease in the apnea/hypopnea index by MAD therapy and the apnea/hypopnea index at baseline. These data and results from another retrospective analysis[45] need further prospective validation.

### *Baseline evaluation*

Before treatment with MAD, a complete medical history including specific questions on sleep habits, and on symptoms related to sleep disturbances is taken. Standardized questionnaires such as the Epworth sleepiness scale[24,25] and other symptom scales[46] may help to estimate the manifestations of sleep-disordered breathing more reproducibly.

A general medical examination, including measurement of body weight and

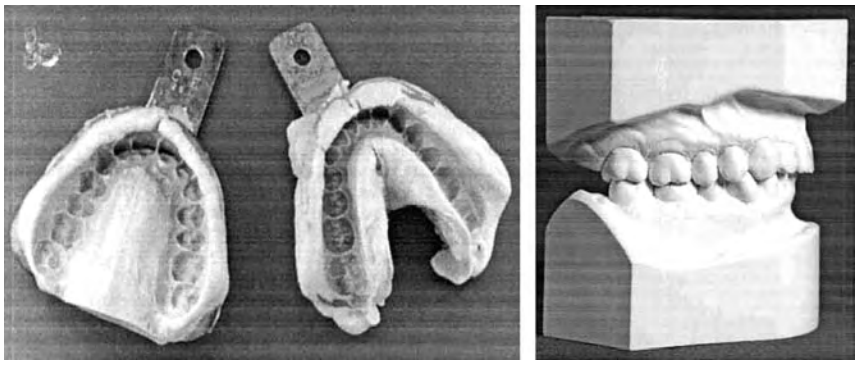


*Fig. 7. a.* Alginate impressions of the upper and lower dentures mounted on an impression spoon. *b.* They are used to fabricate plaster models.

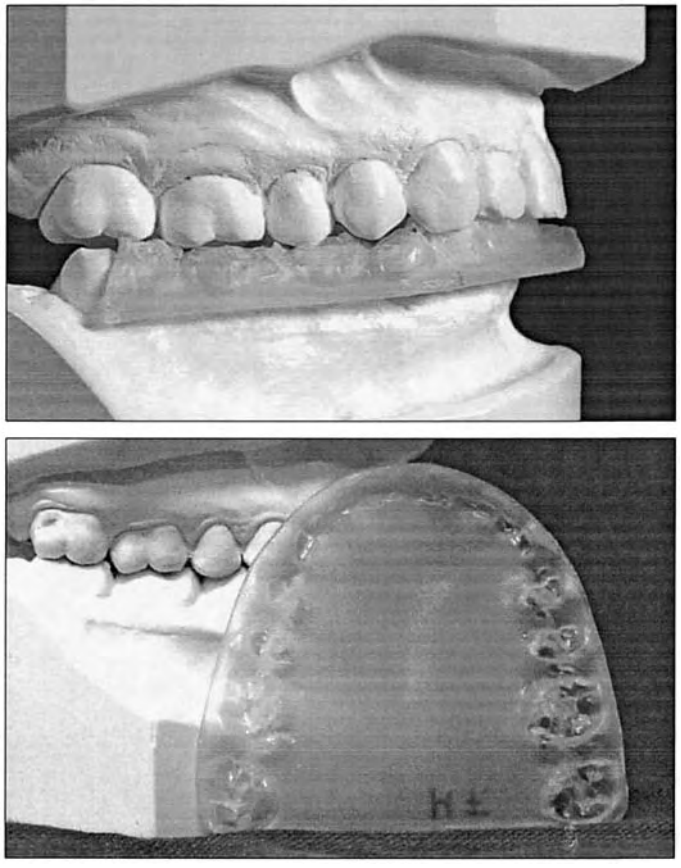


*Fig. 8.* A wax bite obtained by natural occlusion onto a thin sheet of wax documents the relative position of the teeth in the resting position, as a reference for the plaster model and for future comparisons.

blood pressure, is performed. Special attention is paid to factors predisposing to sleep-related breathing disturbances, such as impaired nasal breathing, anatomical obstacles in the upper airway, such as tonsillar and adenoid hypertrophy. If there is any clinical suspicion of hypothyroidism or acromegaly, appropriate laboratory tests are performed.

The dental/orthodontic evaluation includes dental history, inspection of the teeth and periodontium, and assessment of occlusion and of the temporo-mandibular joint. Dental radiographs, cephalography (Fig. 2), plaster models (Fig. 7), and a wax bite (Fig. 8) serve to document the baseline orthodontic status as a reference for follow-up examinations, and for fabrication of the MAD.

The upper and lower dental arches need to consist of at least eight to ten teeth each. Significant pre-existing pain or a reduced range of motion (in particular, reduced protrusion and opening) of the temporo-mandibular joint may preclude MAD therapy. Caries and periodontal disease should be treated before application of a MAD.

*Selection and fabrication of individually fitted mandibular advancement devices*

A large variety of MAD is available on the market. We suggest the use of individually fitted devices which have been evaluated and shown to be effective in prospective, randomized trials (Table 1). The details of MAD fabrication depend upon the specific type of appliance. For the sleep apnea Monobloc and Herbst appliances, as used at the University Hospital of Zürich,[10,34] the first step consists of preparation of plaster models and wax impressions (Figs. 7 and 8). A construction wax bite (Fig. 9) is obtained to define the amount of protrusion and opening to be set in the MAD. In general, initial protrusion is set at 75% of maximal protrusion, corresponding to 7-10 mm. The vertical opening in the front is fixed at 9-12 mm for the Monobloc appliance. For the Herbst appliance, the opening is 4-15 mm. These MAD are made of a methylmethacrylate material and a stainless steel alloy.

After a proper fit of the device has been achieved, the patient can start nocturnal application. An adaptation period of several days to weeks is usually required until the patient is fully accustomed to the use of the MAD. At that time, the effect of the treatment on symptoms and the potential side-effects are assessed. A sleep study with the MAD is performed to judge the objective effect of the MAD on nocturnal respiration and sleep. Adjustments of the protrusion and of other features of the MAD may be required, depending on efficacy and side-effects. In our experience, it may often take several weeks before MAD treatment is optimal. This is one of the drawbacks of MAD in comparison to CPAP therapy, which can be applied without delay.

*Table 1*. Controlled trials of MAD for obstructive sleep apnea syndrome

| Author, year of publication | Type/name of appliance | Study design, number of patients | Outcome measures | Main results |
|---|---|---|---|---|
| Clark *et al*., 1996[19] | Herbst | CX comparison to CPAP,*n* = 21 | Sleep studies | Improved sleep disordered breathing with MAP and CPAP, but to greater degree with CPAP. Patients preferred MAD |
| Ferguson *et al.*, 1996[8] | Snore-Guard | RCX, comparison to CPAP,*n* = 25 | Symptoms, sleep studies | Improved symptoms, and sleep disordered breathing with CPAP and MAD, but to greater degree with CPAP. Patients preferred MAD |
| Ferguson *et al.*, 1997[9] | AdjustableAnterior Mandibular Positioner | RCX comparison to CPAP,*n* = 20 | Symptoms, sleep studies | Similar improvement of symptoms with CPAP and MAD, greater reduction in breathing disturbances by CPAP. Greater patient satisfaction with MAD |
| Bloch *et al*., 2000[10] | Herbst and Monobloc | RCX, comparison of two types of MAD,*n* = 24 | Symptoms, sleep studies | Herbst and Monobloc improved symptoms, snoring, and measured sleep and breathing disturbances, Majority of patients preferred Monobloc MAD to Herbst |
| Metha *et al*., 2001[13] | Mandibular Advancement Splint | RCX comparison to oral plate without protrusion (placebo),*n* = 24 | Symptoms, sleep studies | Improvement in subjective sleepiness, snoring, and in measured sleep and breathing disturbances |
| Engleman *et al.*, 2002[21] | Mandibular Repositioning Splint | RCX, comparison to CPAP,*n* = 48 | Symptoms, sleep studies, vigilance | Greater effect sizes with CPAP than with MAD |
| Gotsopoulos *et al*., 2002[20] | Mandibular Advancement Splint | RCX comparison to oral plate without protrusion (placebo),*n* = 73 | Symptoms, sleep studies, vigilance | Improvement in subjective vigilance sleepiness, objective vigilance, and in sleep disordered breathing |
| Tan *et al*., 2002[22] | Silensor, Mandibular Advancement Splint | RCX comparison to CPAP,*n* = 21 | Symptoms, sleep studies | MAD and CPAP were similarly effective in improving sleepiness and sleep disordered breathing, patients preferred MAD |
| Johnston *et al.*, 2002[23] | Mandibular Advancement Appliance | RCX, comparison to placebo appliance,*n* = 20 | Symptoms, sleep studies | No improvement in Epworth scores by MAD over placebo, but improved sleep disordered breathing |
| Rose *et al*., 2002[27] | Silensor and Karwetzky appliance | RX comparison among two types of MAD,*n* = 16 | Symptoms, sleep studies | Similar symptom improvement by the two MAD, greater improvement in breathing disorders with Karwetzky |

RCX: randomized (R), controlled (C), cross-over (X) trial; MAD: mandibular advancement device

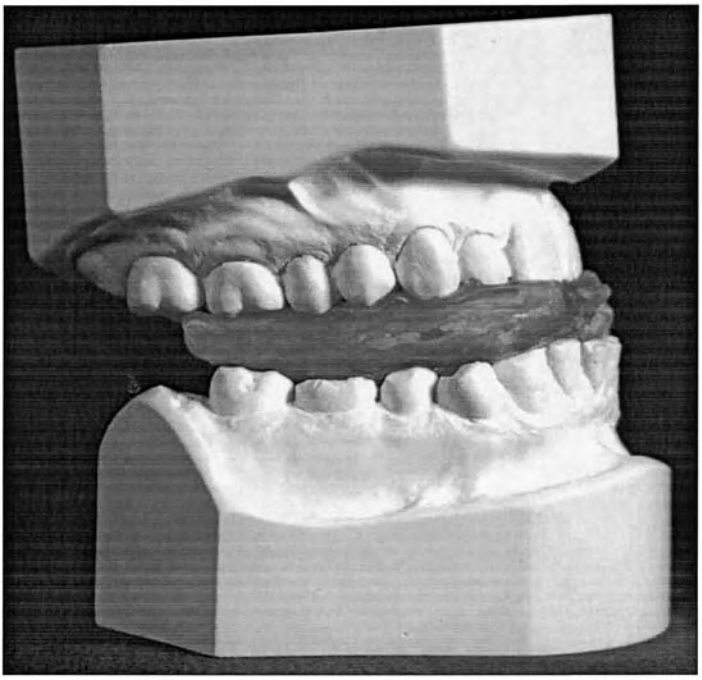


*Fig. 9.* The construction wax bite defines the amount of protrusion and opening to be set in the MAD.

### *Follow-up examinations*

The forces acting on the upper and lower dental arches during long-term MAD therapy may lead to changes in dental geometry and occlusion.[34,35,37] Subtle changes may go unnoticed by the patient. Therefore, regular orthodontic follow-up examinations (for example, at yearly intervals) are recommended to detect such potential side-effects early and to check the integrity of the MAD. Every few years plaster models, wax bites, and cephalographies may be repeated to document potential orthodontic changes precisely, in comparison to the condition before initiation of treatment.

Medical follow-up should ensure the continued effectiveness of the therapy, as assessed by symptom evaluation. This is best performed by means of standardized questionnaires applied repeatedly over time. Depending on the clinical situation (for example, after a significant change in weight), sleep studies with and without the MAD in place may be necessary to objectively evaluate the effectiveness of, and need for, therapy.

## Conclusions

Application of MAD in the treatment of OSAS and simple snoring has been established as a valuable alternative to other forms of therapy, in particular in patients who cannot tolerate nocturnal CPAP ventilation. Results from several randomized, controlled trials suggest that MAD effectively improve symptoms and sleep-related breathing disturbances in OSAS. Since the effect of MAD is variable, and cannot reliably be predicted in an individual patient, a subjective and objective evaluation of treatment efficacy after adaptation of the oral appliance is advisable. As experience with this treatment modality increases, the importance of regular follow-ups during long-term treatment becomes evident to detect potential adverse effects in time. The optimal design of devices to provide maximal efficacy at a minimal risk of side-effects, and the identification of predictors of successful MAD therapy, require further study.

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# VENTILATORY THERAPY IN OBSTRUCTIVE SLEEP APNEA SYNDROME

## Indications and limitations in the treatment of obstructive sleep apnea syndrome

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### Introduction

More than 5% of the world population is affected by obstructive sleep apnea syndrome, also known as OSAS. In order to prevent the irreversible complications that are associated with this syndrome, appropriate therapy is necessary. The elective therapy for OSAS consists of mechanical positive pressure ventilation coupled with a surgical operation, when necessary. Surgery is generally proceeded, and in some cases followed, by ventilation therapy.[1]

The continuous positive airway pressure (CPAP) mechanical ventilators used in therapy are becoming more and more responsive to patients' clinical and daily needs (above all in limiting the side-effects associated with the use of positive pressure).

Mechanical ventilation is an instrumental therapy that, using special equipment, is capable of integrating or even substituting inadequate respiratory function to guarantee aeration.[2] It is indicated in the presence of alterations in ventilation related to respiratory muscle deficiency (deficiency in pumping) and pulmonary pathology (deficiency in aeration, whether or not associated with respiratory muscles fatigue).

The presence of a pressure gradient between the first tract of the airways and the alveoli is necessary to guarantee gas flow.[3] The gradient can be obtained either by positive pressure at the opening of the airways (positive-pressure ventilation) or by producing negative pleuric pressure (negative-pressure ventilation).

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Modern respirators can easily monitor inspiratory and expiratory tidal volume (Vt), inspiratory and expiratory minute volume (MV), respiratory frequency, oxygen flow fraction ($FIO_2$), flow and airway pressure curves with the possibility of showing unproductive efforts, incomplete expiratory flow taking place at the start of a new mechanical action, and positive end-expiratory pressure (PEEP).[4]

The ventilation techniques are divided into total and partial, and can be realized by either the pressometric or the volumetric procedure.

*Pressometric procedure*

With this procedure, airway pressure is the independent variable that can be set on the ventilator by the operator. Vt is the variable dependent upon the mechanical features of the patient's respiratory system (impedance). The ventilator supplies airflow at a pre-established pressure in the patient's airways. The ventilator retains a constant positive pressure within an inspiration time: the flow and volumes supplied depend upon the mechanical characteristics of the respiratory system (compliance and resistance) and therefore vary in relation to the patient's efforts (increase), and in presence of secretions or cough (reduction). This procedure holds less risk for barotrauma, it guarantees better interaction between the patient and the ventilator, but it does not allow a fixed level of minute ventilation to be prearranged, since such a level depends on the mechanical characteristics of the patient's respiratory system.

*Volumetric procedure*

The Vt is the independent variable and is set by the operator. The volume inhaled does not depend on the mechanical characteristics of the patient's respiratory system: it is supplied in a fixed time (inhalation time) and determines the characteristics and pressure range necessary to reach the amount of air to be inhaled.

An intermittent positive pressure-controlled ventilator (completely controlled by the ventilator) or a pressure-assisted ventilator (the patient starts up the ventilator himself using a trigger) is the most frequently used technique.

The ventilator supplies the patient with the necessary gas volume during inspiration, while expiration is passive. This equipment is generally used in the treatment of chronic respiratory failure, both in adults and children with respiratory system pathologies of various etiology.

Total ventilation supports are used when the patient's breathing is completely compromised or when it is pharmacologically interrupted (acute respiratory failure, shock, general anesthesia, coma, polyradiculoneuritis, tetanus). Partial ventilation supports are used to integrate the patient's remaining respiratory function; one of the main applications is during the technique prescribed for acute respiratory failure. An example of partial ventilation support is CPAP,

achieved by a completely spontaneous mode in the presence of PEEP. Non-invasive methods simplify this type of ventilotherapy and show long-standing improvement in aeration. One of the main feature of the procedure is the ventilator's connection to the patient by means of facial or nasal masks. The mask must fit perfectly to the patient's face in order to avoid gas loss that could decrease or nullify the effectiveness of the therapy, and cause serious consequences due to hypoventilation.[5]

In a study conducted in France in 1994, 300 patients were treated with a positive pressure ventilator using a nasal mask. It was noted that, after their usual mask had been replaced by a different one, characterized by a larger dead space that caused a reduction in the positive effects of mechanical ventilation, three of ten patients went into acute respiratory failure.

The main aim of our work is to identify which therapeutic aid minimizes the risks and emphasizes the benefits for the patient.

## Material and methods

In OSAS therapy, the ventilator maintains positive pressure throughout the respiratory cycle (inspiration and expiration); in most cases, a nasal mask is used. Positive pressure keeps the first tract of the airways pervious, and increases functional residual capacity (FRC). The aim of the system is to maintain pre-selected and stable positive pressure throughout the respiratory cycle, while the flow and the volume, produced during inspiration, are generated by the patient's respiratory muscle activity. We can identify three types of systems that supply CPAP, as follows:

1. a continuous free-flow system powered by high or low pressure gas;
2. a continuous flow system originating from turbine powered ventilators;
3. a demand flow system.

The continuous flow system set must be equipped with a gas-mixer, a humidifier, and a water valve reservoir for the PEEP. The CPAP monitoring set includes $SaO_2$, a value alarm for the PEEP, and capnometry capable of reporting apneas, disconnection, rebreathing episodes, poor tolerance, and respiratory frequency. Clinical control of tolerability is important; changes in frequency, tenseness, sweating, and tachyarrhythmia force the therapy to be interrupted. CPAP treatment should reduce the onset of obstructive apneas, improve the quality of sleep and performance during the day, and reduce cardiovascular complications related to this pathology. It is not easy to achieve these goals because, even with OSAS, CPAP cannot always be prescribed: the pathology stage and general clinical conditions of the patient must be evaluated.

To use CPAP correctly, it is necessary to determine a PEEP able to:

- eliminate/reduce rhonchopathy in the patient's various decubitus during sleep;
- reduce the apnea/hypopnea index (AHI);

- eliminate/reduce micro-reawakenings and/or reawakenings caused by respiratory events;
- restore a normal hypnogram;
- eliminate/reduce respiration with flow limitation.

In our department, we treated patients affected by OSAS with positive pressure ventilatory therapy (nasal PAP (nCPAP), bi-level PAP (BPAP), and auto CPAP (ACPAP). One hundred patients were examined after the appropriate screening tests (pulsoximetry, polysomnography, and an anamnestic questionnaire). Eligibility for this therapy depended on the patient's respiratory disturbance index (RDI). Two conditions were considered in particular:

1. 5<RDI<30 with symptoms characterized by snoring, daytime sleepiness, fragmented sleep associated with micro-reawakenings, modifications in behavior, and mood disorders.
2. RDI> 30 with complications and symptoms involving the respiratory and cardiovascular systems.

We excluded the use of CPAP in mild OSAS (RDI<5) because, in such cases, the risks did not justify the benefits. In fact, in patients with respiratory system diseases in whom the increase in respiratory work (WOB) necessary to complete the expiration could result in dyspnea, anxiety, and uneasiness, and could therefore reduce compliance following appropriate evaluations (type of patient and pathologies), we used two other types of positive pressure ventilators: BPAP and ACPAP.

Based on the assumption that the pressure required to maintain the upper airways open can be different during inspiration and expiration, the bi-level ventilator works on two Paw levels (airway pressure): the highest level supports inspiration (IPAP) and the lowest one supports expiration (EPAP).

Bi-level ventilation can take place in either the spontaneous (assisted) or the timed (controlled) mode. The assisted mode, in which inspiration and expiration are initiated by the patient's way of breathing, is the one used in OSAS therapy. IPAP must ensure adequate Vt and adequate respiratory frequency. The respiratory cycle starts at a pre-selected air flow value, while the expiration starts when the inspiratory flow decreases and reaches a fixed level (about 30% of maximum inspiratory flow). In the initial stage, the inspiratory and expiratory pressure is settled at 2-3 cm $H_2O$ and it is progressively increased until the apneas disappear; and only later is the inspiratory pressure raised in order to eliminate snoring and hypopneas.

The two pressure levels are able to improve both the dyspnea and the ability to perform physical exercise by reducing the elastic load caused by pulmonary hyperinflation and positive end expiration pressure, and by increasing blood flow.

The use of BPAP allowed us to differentiate the pressure applied during the phases of the respiratory cycle, and was shown to be effective in the treatment of obstructive apnea, overlap syndromes, chronic obstructive pulmonary disease (COPD), restrictive pathologies, neuromuscular pathologies, and in all

those cases in which high pressure was necessary (generally >10-12 cm $H_2O$).

ACPAP automatically sets the respiratory pressure in reply to flow variations (apneas/hypopneas or flow limitation) and/or to the intensity of the snoring. It is supported by two pressure levels: a minimum value and a maximum one, within which the patient's respiratory pressure variations can take place. It is preferentially used in patients with poor compliance to CPAP treatment, in OSAS patients with episodes of apnea/hypopnea taking place for limited periods during sleep, often in strict and exclusive association with the REM phase.

Efficacy was similar to that obtained with CPAP treatment. The average pressures produced with ACPAP were lower than those produced with CPAP, and its utilization reduced the general cost of patient management. Limitations identified were the absence of cardiac rhythm disorder monitoring and a documented increase of central apneas in patients treated.

In addition to the various types of ventilators, computerized control systems are available to optimize the use of positive pressure ventilation in apneic patients. Among these, it is important to highlight the recent use of new digital systems that automatically regulate the sensibility of the respiratory trigger and of the expiratory cycle in the presence of air losses in the circuit.

Measured and calculated values include: IPAP, EPAP, total respiratory frequency, Ti/Ttot, Vt, minute ventilation, peak inspiratory flow, percentage of the cycled acts, and air losses.

Ventilation therapy has been administered by means of two types of interface patient-ventilator systems:

- nasal (standard, moldable classic silicone gel, closely adaptable to the nasal profile) (profile-lite mask), the Adam system formed by two silicone nasal cushions adaptable to the nostrils);
- facial or oronasal (conventional, orthodontic).

## Results

After six months of therapy, we observed that the ventilation therapy produced immediate (during use) and delayed effects on the patients studied:

*Immediate effects*

- modification of the first tract of the airway morphology.

*Delayed effects*

- modification of the first tract of the airway morphology;
- reduction of sleep fragmentation;
- modification of genioglossus muscle functionality with an increase of muscular activity after CPAP mechanical stimulation of the mediated receptors;
- better ventilation control.

After constant night-long therapy for at least five days a week for six months, treated patients showed:
- reduction in/ending of snoring;
- improvement in cognitive skill and psychological function;
- increase in $PaO_2$, reduction in $PaCO_2$ and hematocrit;
- improvement in quality of life;
- increase in testosterone secretion;
- increase in somatomedin C with a secondary rise in growth hormone levels;
- increase in striated muscle activity due to better autonomic nervous system response;
- improvement of symptoms in gastroesophageal reflux disease;
- reduction in adrenaline and aldosterone secretion;
- reduction in diastolic and systolic pressure;
- improvement in functionality of right and left ventricles.

Factors influencing ventilotherapy use were:
- reduction of patient compliance;
- side-effects.

Compliance was influenced by the type of mask used, ventilator acceptance (too noisy a ventilator and wrong use of the humidifier), and by adaptability to pressure. Silicone gel nasal masks were accepted best. The criteria for comfortable and tolerable masks were: stiff frame with a silicone cushion to guarantee the best possible adhesion to the patient's face, revolving unfixed mask-ventilator connector (to enable the patient to move more freely), a cap associated, when needed, to a chin rest in order to avoid mouth opening during night-time. When the nasal mask could not be tolerated, we used other systems such as the profile-lite mask and Adam system. We also examined the most frequently noted advantages and disadvantages regarding the use of facial and nasal masks:

*Nasal mask*

Advantages:
- freedom of speaking, eating and drinking;
- less risk of inhalation in case of vomiting;
- less risk of aerophagy;
- less risk of claustrophobia.

Disadvantages:
- loss of air from the mouth;
- imperfect adhesion in the absence of teeth or dental prosthesis.

*Facial mask*

Advantages:
- no loss of air from the mouth;

- better use in the absence of teeth.

Disadvantages:

- interference with speaking, eating and drinking;
- increased risk of inhalation in case of vomiting;
- increased risk of claustrophobia and aerophagy.

Humidification of airways played an important role when unpleasant side-effects occurred (oronasal dryness, epistaxis), which affected patient compliance (in the absence of prompt intervention, up to 40% of patients).

We verified that compliance increased when:

- the patient was appropriately instructed on the characteristics and importance of the therapy;
- in order to minimize loss of flow from the mouth, the patient himself tried on and chose the mask that fitted him best;
- the pressor set-up was monitored and an incorporated humidifier system was used;
- the possible onset of side-effects was supervised.

The most frequent side-effects were:

- cutaneous lesions located at the contact areas between the facial skin and the profile of the mask (around the nose and mouth);
- conjunctivitis and ocular flare (caused by loss of air due to imperfect adhesion);
- rhinitis (caused by excessive dryness of the ventilated air).

## Conclusions

Our observations show that each ventilation method must be evaluated in relation to the patient's clinical situation and compliance rate. Increased attention and more detailed knowledge of this pathology, together with improved efficacy of the therapy, are the main factors that will contribute to improving the symptomatological and clinical state of these patients.

We cannot yet identify any ventilator as being 'ideal', but rather they should be considered useful therapeutic aids which should be prescribed by a skilled physician after careful assessment of the patient's clinical condition and stage of disease, and, above all, of the risk and benefit analysis of such a therapeutic approach.

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# CONTINUOUS POSITIVE AIRWAY PRESSURE COMPLIANCE IN OBSTRUCTIVE SLEEP APNEA SYNDROME PATIENTS

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## Introduction

Continuous positive airway pressure (CPAP) is the medical gold standard and ideal first line treatment in moderate to severe obstructive sleep apnea (OSA).[1] First described in 1981, nasal CPAP (nCPAP) is a safe therapeutic option with few contraindications or serious side-effects.[2] nCPAP is a symptomatic therapy and cure is rare.[3] Therefore, questions arise on long-term compliance, and this article reports on our experience with CPAP compliance.

## Methods

We studied 69 patients with OSA of variable degrees: 48 had chronic obstructive pulmonary disease (COPD), six of whom suffered from alveolar hypoventilation (overlap syndrome) and were treated with mechanical ventilation (VM) and bi-level; 63 patients were evaluated for CPAP and demand PAP (DPAP) compliance. There were 40 males and 23 females with a mean age of 50 years. Forty-two were obese (25 males and 17 females) with a mean BMI of 26 kg/$m^2$. All patients were subjected to overnight sleep study with the Night Watch Healthdyne Polysomnograph (USA) and followed a two-phase protocol. During phase I, diurnal VM tolerance, supervised by physicians, was followed by overnight CPAP at low pressure (5 cm $H_2O$). The next day (phase II), diurnal adaptation with variable pressures, ranging from 7-9 cm $H_2O$, preceded customized nocturnal monitoring and pulse oximetry recording. After each session (diurnal and nocturnal), we asked whether the patients had experienced any benefit from CPAP.

The patients were empirically divided into four groups, according to the

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*Table 1.*

A = 10-20 AHI
B = 20-30 AHI
C = 30-50 AHI
D = >50 AHI

*Table 2.* CPAP compliance

| | *No. of patients* | *Diurnal tolerance 5 cm $H_2O$* | *Nocturnal tolerance 5 cm $H_2O$* | *7-9 cm $H_20$ + pulse $O_2$* | *6 months' compliance* | *6-12 months' compliance* |
|---|---|---|---|---|---|---|
| A | 28 | 21 | 18 | 13 | 0 | 2 |
| B | 12 | 9 | 8 | 8 | 4 | 3 |
| C | 8 | 7 | 7 | 7 | 5 | 3 |
| D | 10 | 9 | 9 | 9 | 8 | 6 |

*Table 3.* DPAP compliance

| | *No. of patients* | *Diurnal tolerance* | *Nocturnal compliance* | *6 months' compliance* |
|---|---|---|---|---|
| A | 1 | 1 | 1 | 1 |
| B | 1 | 1 | 1 | 1 |
| C | 2 | 2 | 2 | 2 |
| D | 1 | 1 | 1 | 1 |

degree of the disease, based on the apnea-hypopnea index (AHI), as shown in Table 1. The results of CPAP compliance are summarized in Table 2. Five patients were also monitored for DPAP compliance (Table 3).

## Discussion

The incidence of OSAS ranges from 1-4% and represents 90% of sleep disorders. Sleep breathing disorders include upper airway resistance syndrome (UARS) and OSAS. Obstructive sleep apnea was discovered in the search for the pathophysiological process underlying the Pickwickian syndrome by nocturnal polygraphic examination of abnormal sleep activity. It has been shown that OSAS has consequences on cognitive functions, cardiovascular sequelae, including hypertension, cardiovascular accidents, cardiac arrhythmias, and myocardial infarction. It also decreases work performance and psychomotor vigilance, resulting in as much as a seven-fold increased risk of motor vehicle accidents.[4]

nCPAP is recognized as the best 'symptomatic' treatment for OSAS. Short-

and long-term compliance is directly related to the improvement of symptoms. In contrast with previous reports, in the last few years, studies based on masked monitoring demonstrated that the effective use of CPAP during periods of up to three months was poor, only approaching 50%.[1] Recent innovations in positive airway pressure (PAP) delivery, such as bi-level and DPAP which allow patients to titrate the pressure in an effort to reduce the level of discomfort, have only provided a slight improvement in the compliance rate compared to CPAP.[5]

It is not easy to verify which indicators correlate better with long-term compliance, and the literature is somewhat controversial. Some authors[6] showed correlations between compliance and parameters such the apnea-hypoapnea index (AHI) and oxygen saturation during sleep. Some have found links with daytime somnolence,[7] while others reported no correlations. Our experience suggests that the level of the patient's education and intelligence also plays an important role in the acceptance of nasal PAP delivery. Our limited data on DPAP (five patients) seem promising, but provide no statistical evidence. However, long-term compliance with nCPAP is probably related to many variables.

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# NASAL POSITIVE AIRWAY PRESSURE

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Nasal positive airway pressure (NPAP) is a simple, effective, non-invasive technique for treatment of upper airway obstruction during sleep.

The sleep specialist's role in introducing NPAP to the patient is two-fold. One is to perform a sleep study, monitoring patient response and establishing the optimum pressure needed to maintain an open airway. The other is to support the patient through the potential obstacles of NPAP therapy.[1] With the advancement of technology and various methods available for NPAP therapy, treatment can be quite simple, for the patient as well as for the sleep specialist.

NPAP acts primarily by providing a physical 'pressure' splint to the upper airway. The key feature of NPAP is that it elevates the pressure in the oropharyngeal airway, thus reversing the transmural pressure gradient across the pharyngeal airway.

Once a diagnosis of sleep apnea has been established, the patient is scheduled for a second night of study. A demonstration of NPAP should be performed prior to study as this helps to reduce the stress or anxiety usually felt by the patient. This will permit proper sizing of the mask, and allow the patient to become comfortable with the system.

Various types of NPAP devices are now available for use. The standard and widely used device is continuous positive airway pressure (CPAP). Another device is the bi-level positive airway pressure (BPAP). The newest device to reach the public is the auto positive airway pressure (APAP), also known as 'smart CPAP'.

The goal of the sleep technologist performing the overnight NPAP study is to obtain the optimal pressure needed to reduce the respiratory disturbance index (RDI) to ≤5/hours of sleep, eliminate oxygen desaturations, maintain the $S_aO_2$ above 90%, reduce/eliminate respiratory arousals, eliminate snoring, and eliminate paradoxical diaphragmatic breathing. This should be completed for all stages of sleep and all body positions.

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CPAP provides a continuous flow of positive pressure on inspiration and expiration, allowing for one pressure setting. CPAP provides immediate and effective non-invasive treatment for the obstructive sleep apnea syndrome (OSAS). CPAP has been known to improve quality of life, allowing the patient to have a good quality night's sleep.

Although CPAP is an immediate and effective form of treatment for OSAS, compliance has been a growing concern for the sleep specialist. The major complaint of the CPAP patient is the inability to exhale against the constant pressure, thus creating a sensation of dyspnea. The average nightly use of CPAP is 4.8 hours.[1] This being at the beginning of the night, while the therapy is most needed at the end of the night when rapid eye movement (REM) is the longest.

BPAP provides a dual flow of continuous positive pressure at two different levels: inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP). This requires two different pressure settings. BPAP is best used for patients who have compliance issues, such as the inability to exhale. BPAP allows for a lower expiratory pressure setting, thus making it easier to breathe. BPAP can also be used for patients who have insufficient ventilation issues while sleeping, *i.e.*, chronic obstructive pulmonary disease (COPD), or neuromuscular disorders such as amyotrophic lateral sclerosis (ALS) or kyphoscoliosis. The greater the difference in the IPAP and EPAP pressures (also known as the delta), the better the ventilation. A backup respiratory rate can also be added, thus making it a ventilator. Although BPAP is better tolerated than CPAP, guidelines enforced by Medicare have made it difficult to use BPAP for compliance issues.

APAP or 'smart' CPAP provides a continuous flow of positive pressure on inspiration and expiration, with changes in the level of pressure to meet the patient's needs. The patient's needs are to eliminate apneas, hypopneas, and snoring in all sleep stages and body positioning. The disadvantage is that it is assumed when the respiratory events are eliminated the $S_aO_2$ is stabilized. This is not always true. APAP allows for night-to-night variability, the patient may need higher pressures one night compared to another night, perhaps some alcohol was ingested. APAP allows for sleep stage variability and body positioning variability; the patient might need higher pressures in REM than in non-REM, or higher pressures while in the supine position as opposed to the lateral position. Sleep quality is slightly, if not significantly, better, patient compliance is highly significantly better.[2] Further studies are necessary in order to define the patient group for which such a therapy would be useful.[3] APAP is more expensive and, with the lack of adequate research, this form of therapy is difficult to obtain in the USA.

It is the sleep technologist's responsibility to ensure the patient's compliance during the overnight sleep study. This is accomplished by being able to recognize issues that could lead to non-compliance, such as, several awakenings, feeling short of breath, pulling at the mask, removing the mask, or any complaints put forward by the patient.

It is the technologist's responsibility to correct the issues of non-compliance, whether this be a little consoling from the technologist or a change in the equip-

ment. Something as simple as changing the style of mask, adding humidity or a chin strap, or even changing the type of pressure generator, can help a study to be successful.

The effectiveness of NPAP has been documented as a viable alternative for the treatment of sleep apnea when used on a regular and permanent basis. It is also applicable as a temporary measure while awaiting surgery, or even as a postoperative treatment during the healing process. Furthermore, NPAP offers a form of instant treatment for the patient with life-threatening sleep apnea.

It is our role as sleep specialists to provide treatment options for the patient with OSAS, whether this be a surgical or a non-invasive method. If a non-invasive method is chosen, we should encourage the acceptance of NPAP therapy through attentive initiation, education, support, and outcome, in order to meet the needs of our patients.

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# EFFECTIVENESS OF NONSURGICAL THERAPY IN EARLY OBSTRUCTIVE SLEEP APNEA

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## Introduction

Patients with early obstructive sleep apnea syndrome (OSAS) often suffer from mild symptoms during the daytime, but their snoring disturbs their immediate surroundings. Surgery can cure these symptoms in up to 80%.[1-3] A substantial number of patients cannot undergo surgical therapy because of the high risk of intra- or postoperative complications, or they reject this option completely. The objective of this study was to evaluate the effects of drug therapy with theophylline compared to nasal continuous positive airway pressure ventilation therapy (nCPAP) in early OSAS.

## Patients and methods

Twenty-five patients aged between 27 and 50 years (mean, 38 years), who were not eligible for surgical therapy and who presented with early OSAS with a respiratory disturbance index (RDI) of up to 28/hour, were randomized into two groups. Group 1 (theophylline) consisted of 12 patients to whom a nocturnal oral dose of 5-7 mg/kg body weight theophylline was administered. Blood samples were taken intermittently to monitor the theophylline serum level. Group 2 (nCPAP) consisted of 13 patients. The body mass index of all patients was a mean of 26.6. Rhinomanometric nasal obstruction was moderate in all cases. All patients were evaluated using the Epworth sleepiness scale (ESS). Polysomnography was performed at the start of the trial and after five to 12

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weeks, or at the time when the patients left the trial. Changes in RDI and ESS were decisive for evaluation of the results of the therapy.

## Results

In eight of the 12 patients in the theophylline group, there was an improvement in RDI as confirmed by polysomnography. Seven of the 12 patients reported a subjective improvement of their symptoms. Their mean RDI dropped from 23.5-19.8; mean ESS fell from 9.9-8.3. There was 66% of responders in the theophylline group. The mean reduction of RDI in this subgroup was 33%. In the non-responder group, RDI increased by up to 40% during the trial. Serum theophylline levels monitored were 5.2–8.8 μmol/ml.

In the nCPAP group, there was a significant decrease in RDI from a mean of 23.2-2.9. The ventilation pressure applied was a maximum of 8 mbar. The CPAP group was divided into three subgroups, as follows: *1.* responders using the device regularly (38.4%); *2.* patients not using the device regularly (30.7%); and *3.* patients who rejected the device (30.7%). The highest ventilation pressure was applied in the responder group. Reasons for complaints were: discomfort (61%), noise (38%), mask fitting (30%), rhinitis, conjunctivitis, complaints from their partner (15.3%).

## Discussion

Various therapy options for patients not eligible for surgery in early OSAS are described in the literature.[4-6] Results concerning the use of theophylline are conflicting.[7-9] Our study demonstrates that the effect of theophylline is mild to moderate in early OSAS. Serum theophylline levels confirmed regular use of the drug. In the dose administered, we noted no major side-effects, and the drug was well tolerated in all cases after adjustment for the correct dose. We saw no significant impairment of sleep quality, and ESS improved. At present, there are no reliable indicators to predict the individual success of theophylline therapy. Therapy has to be carefully monitored because of the possibility of impairment in non-responders. Drug therapy with theophylline could be an alternative in patients who reject other options, when there are no contraindications. nCPAP is potentially highly effective in early OSAS, but its acceptance level of 38% was substantially lower than that for theophylline therapy (100%), or than that for CPAP in severe disease (60-80%).[10-12] The side-effects of CPAP therapy, which are acceptable when the disease is severe, are often not tolerated in early OSAS.

From this study, we can conclude that nonsurgical therapy has to be planned very individually in early OSAS. An effective and tolerable nonsurgical long-term strategy is still lacking in the majority of patients with early OSAS.

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# HIGHLIGHTS ON NONSURGICAL THERAPIES

# EFFECT OF THE MODIFIED 'TWIN BLOCK' DENTAL APPLIANCE ON OBSTRUCTIVE SLEEP APNEA SYNDROME

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## Introduction

Oral appliances may be effective in reducing the severity of obstructive sleep apnea syndrome (OSAS),[1,2] based on advancement of the lower jaw and enlargement of the retropharyngeal space. The aim of this study was to evaluate the clinical efficacy of an original dental appliance on a group of snorers affected by OSAS in various degrees.

## Methods

Thirty consecutive snorers admitted to our outpatient clinic between February and July 1999 were submitted to the following evaluations: clinical history; physical examination; ENT and orthodontic evaluation; and nocturnal polysomnographic recording (PLSG). Inclusion criteria were as follows: aged between 20 and 70 years; mild to moderate daytime sleepiness (Epworth sleepiness scale 10-15/24); apnea index >5; dentition able to retain an oral appliance. Exclusion criteria were as follows: BMI >40; structural nasal and/or oropharyngeal abnormalities; drug or alcohol abuse. Orthodontic treatment was with the so-called 'twin block' oral appliance;[3] the original device was modified by adding a screw system able to create a measured advancement of the lower jaw, and four additional clasps to stabilize the construction bite. The dental appliance was adjusted within the first 15 days, in order to advance the lower jaw up to 75% of its maximal protrusion,[1] according to patient tolerance. After adapta-

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tion, it was suggested that patients should wear the oral device for the whole night, every night. After a minimum of 30 days, all the patients were re-evaluated clinically, orthodontically, and by nocturnal PLSG, while wearing the oral device. The results were compared with baseline data; statistical significance was evaluated by the Fisher exact test and the Mann-Withney test for non-parametric data.

## Results

Seven subjects were included in the study: five suffered from mild OSAS, while the remaining two both had severe OSAS, but had refused treatment with nasal continuous positive airway pressure (CPAP). The mean age was 48 ± 7 years; mean BMI 27.1 ± 3.5; mean percent predicted neck circumference 102 ± 3. All patients reported good tolerance to the device and no significant side-effects were mentioned. After application of the oral device, a witnessed reduction of snoring was reported in all cases. The total number of nocturnal desaturation episodes significantly decreased (301 ± 212 versus 45 ± 36; $p < 0.05$); the apnea index also decreased (14.6 ± 10 versus 6.6 ± 7.4), but the reduction was not statistically significant.

## Conclusions

The modified twin block oral appliance is effective in reducing snoring and improving the nocturnal ventilatory pattern in mild OSAS. This appliance could also be adequate for patients with severe OSAS who will not comply with nasal CPAP, but this hypothesis still needs to be confirmed by prospective controlled trials.

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# OBSTRUCTIVE SLEEP APNEA SYNDROME AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

## Correlation and treatment of these two pathologies in the overlap syndrome

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The overlap syndrome is characterized by the obstructive sleep apnea syndrome (OSAS) being associated with chronic obstructive pulmonary disease (COPD); it is found in 10% of COPD patients. The distinction between 'single' and 'pure' OSAS patients and overlap syndrome patients is very important, not only for clinical or prognostic implications, but also for treatment.

It is not possible to mark out a causal line to compare the two pathologies, but it is certain that more than a few OSAS patients suffer from associated chronic obstructive disease of the airways.

Therefore, COPD must always be checked for in OSAS patients. Patients with an overlap syndrome have hypoxia, hypercapnia, and pulmonary hypertension, also noticeable in mild bronchial obstruction. They are at greater risk of developing respiratory insufficiency and cor pulmonale. This theory is supported by an important study, published in France in 1995, which shows that patients with associated syndromes had diurnal $CO_2$ partial pressure in the arterial blood ($PCO_2$) and a median pulmonary artery pressure higher than other patients, while they had lower $O_2$ partial pressure in the arterial blood ($PO_2$). Moreover, median pulmonary pressure was higher at rest and during steady-state exercise.

Researchers point out that the patients examined were heavy smokers and therefore were at a higher risk of developing respiratory insufficiency. On the basis of these considerations, our interest in OSAS, which is a fascinating facet of medical science, was essentially motivated by monitoring the clinical condition of patients who had already been treated for an obstructive disease, and in whom there had been a change in the clinical and pathological pattern.

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COPD is a complex, heterogeneous clinical syndrome, defined on a functional basis as being the progressive reduction of maximum expiratory flows, with an increase of expiratory residual volume (ERV), as the consequence of a chronic inflammatory process which causes the variable coexistence of chronic bronchitis, emphysema, and chronic asthma. The reduction of maximum expiratory flows (assessable by FEV1/VC ratio), both chronic and progressive, can link up with airway hyperreactivity, and it is only minimally or partially reversible with the appropriate treatment.

It is found in 20% of the adult population. According to official records, males are affected more frequently than females. Nevertheless, the prevalence of COPD is also rising in females because of the increasing tendency of women to smoke.

Since all the physiopathological events that promote the onset of sleep apnea are derived from sleep, it would seem appropriate here to describe the sleep of a COPD patient.

What happens to a COPD patient during sleep? What mechanisms provoke the onset of OSAS in COPD patients?

The variations in respiratory functions are qualitatively similar to those of a normal subject, but are quantitatively accentuated in such a way that they affect the clinical and physiopathological aspects of the main disease.

Alongside these characteristics, we find alterations in the starting and preservation of sleep, with a reduction of total sleep time, especially of deep sleep (stages 3 and 4 NREM), as a consequence of its fragmentation due to frequent re-awakenings, determined by respiratory disorders (productive cough, dyspnea), the side-effects of some drugs, and also, according to some authors, the alterations of gas exchanges. The main alteration is represented by hypoventilation caused by a reduction in tidal volume and minute ventilation, which is associated with irregular and superficial breathing during the rapid eye movement (REM) phase.

Factors determining hypoventilation are as follows:

- reduced motility of the chest, due to alteration of the contractile function of the intercostal and inspiration accessory muscles, not compensated for by activity of the diaphragm which, having lost its curvilinear shape and assumed a flattened one, is not able to ensure effective contraction for lung expansion during inspiration;
- reduction of the neuromuscular respiratory output and ventilatory response to blood gas alterations and to a rise in resistance, due to an increase in upper-airway flow resistance and to mucus retention in the peripheral airways caused by alteration in the cough reflex;
- the possibility of paradoxical movements (thoracic retractions during inspiration as a consequence of asynchrony between the intercostal muscles and the diaphragm and/or a rise of upper-airway resistance during snoring);
- alteration in the ventilation/perfusion ratio, with a rise in the shunt fraction during the REM phase, also caused by reduction of lung volume, which is

associated with a reduction of functional residual capacity (FRC) and determines an increase in closing volume.

Hypoventilation is the main cause of the reduction of oxyhemoglobin saturation (especially during the REM phase). The reduction of oxyhemoglobin saturation during sleep is more accentuated among patients who are blue bloaters (presenting with hypoxemia and hypercapnia during waking hours) compared to those who are pink puffers (normocapnic during waking hours).

Significant desaturation also occurs in patients who have no serious hemogasanalysis alterations during waking hours: these subjects are classified as desaturators and, in various follow-up studies, have often been compared to patients with similar hemogasanalysis values, but without desaturation during sleep (non-desaturators).

The prevalence of episodes of nocturnal oxyhemoglobin desaturation depends on different criteria used in various studies examined. Nocturnal hypoxemia occurred in 27% of patients with a daytime $PaO_2 > 60$ mmHg, in 68% of patients with a median FEV1 of 43% of normal values, in 100% of patients with an FEV1 < 26% of predictive values, in 67% of subjects with a $PaO_2$ of 55-69 mmHg and a FEV1 of about one liter while awake.

Fletcher and co-workers[1] consider desaturation to be significant when oxygen saturation is less than 85%, for a time of > 5 minutes in patients with an $O_2$ saturation of at least 90% during waking hours. Another suggested criterium is to define desaturation as the reduction of $SaO_2$ under 90% for > 30% of the registration time, *i.e.*, time in bed (TIB).

It would be relevant to consider the following parameters as being predictive:

- $SaO_2$ during waking hours and during the night
- $PaO_2$ determined by hemogasanalysis
- FEV1 determined by respiratory dynamic function tests (spirometry)
- ventilatory reply to hypercapnia
- ventilatory reply to hypoxia
- $SaO_2$ during physical exercise or walking test
- BMI>28
- $PaCO_2 > 50$ mmHg

The practical problem with these patients is to understand the predictive importance of $PaO_2$ while they are awake, in relation to nocturnal $SaO_2$. Various studies show that the predictive value of daytime $PaO_2$ is seldom reliable, but that daytime hypoventilation seems to represent an important factor for inducing hypoventilation during sleep.

The consequences of oxyhemoglobin desaturation can have an effect on:

- *Pulmonary circulation:* pulmonary hypertension can occur during the REM phase, and also during oxyhemoglobin desaturation in patients with normal oxygen values of the arterial blood in the awake state. The reduction of $SaO_2$ during the REM phase could induce cor pulmonale, but it is not certain whether this complication occurs in the absence of hypoxemia during

waking hours. Recent research regarding endothelin-1 (ET1) in COPD patients shows a relationship between hypoxemia and ET1 increase in both patients with $SaO_2 < 85\%$ and non-desaturators. Other authors excluded this possibility, considering that the hypoxemia during the REM phase was a risk marker for the future development of pulmonary hypertension.

- *Systemic circulation:* considerable increases in arterial pressure have been detected during episodes of nocturnal hypoventilation and the consequent reduction of $SaO_2$. Arterial hypertension, tachycardia, and hypoxemia could all increase myocardial demands in conditions of reduced oxygen supply, despite the autoregulated mechanisms of coronary blood flow attempting to offset these effects. These patients have a high risk of mortality.
- *Hematopoietic system:* prolonged duration $SaO_2$ under 85% can provoke an increase in red blood cells; in such patients, erythropoietin is increased during the night as well as in the morning, particularly in patients with $SaO_2$ under 60%.
- *Cardiac rhythm:* hypoxemia is a recognized cause of ventricular ectopic beats.

In COPD patients, the basic treatment is long-term oxygen therapy (LTOT), associated with non-invasive mechanical ventilation in some cases. This treatment is mainly realized by the use of intermittent positive pressures (BiLevel-PAP), or by continuous positive pressure ventilators (CPAP). The main indication is in hypoxemic and/or hypercapnic patients.

According to some authors, results regarding sleep quality include improvement of total sleeping time and sleep efficiency (TST/TIB), greater efficacy of gas exchanges due to an increase of chemoceptors or to a reduction of respiratory work caused by reduced engagement or respiratory muscle fatigue. These results were not unanimous, since some studies reported a better therapeutical effect from the use of monotherapy oxygen, despite the use of ventilatory support alone or in association with oxygen administration.

Other therapies involved the use of anticholinergic drugs (inhalation of ipratropium bromide), which seem to improve bronchial obstruction indexes, quality of sleep with fewer re-awakenings, to prolong the REM phase, and to improve blood oxygenation, and the use of protriptiline which reduces the REM phase, improving oxyhemoglobin saturation. Debates are ongoing on the use of theophylline, $\beta_2$-stimulant agents, and almitrine.

In our Respiratory Physiopathology Unit, we studied 100 COPD patients who reported sleep disorders. Very complex clinical patterns appeared to be associated with other pathologies, usually because these patients were affected not only by respiratory sleep disorders, but also by other pathologies already under treatment, such as arterial hypertension.

On the basis of anamnesis, physical examination, clinical pattern (considering the symptoms referred), an informative questionnaire, and noninvasive oximetric monitoring at night and during the day, the patients were subjected to nocturnal out-patient polysomnography.

## Material and methods

A polysomnographic system (Polimesam) enabled the monitoring of cardiac frequency variations by ECG, oxyhemoglobin saturation, orinasal airflow, limb movements and body position, thoracic and abdominal respirogram, the presence of rhonchopathy, and eye movements by electro-oculogram.

Eighty-three males and 17 females, with a median age of 61 years (range, 23-80 years), entered the study.

Various pathologies, excluding respiratory diseases, occurred as follows: 61% essential arterial hypertension; 31% obesity; 15.9% dyslipidemia; 13% pathologies of the first tract of the airways; 6.8% type 2 diabetes mellitus.

Anatomical and functional alterations of the upper airways were evaluated by otorhinolaryngological counselling; 60% of these patients presented with difficulties regarding breathing through the nose, 20% of whom had approached our unit after surgical treatment. The most frequent alterations were macroglossia often associated with obesity, hypertrophy of the turbinates, and deviation of the nasal septum.

After polysomnography, it emerged that 30% of the patients were suffering from nocturnal apnea syndrome.

### *Clinical symptoms*

The most frequently noted symptoms were:

- rhonchopathy in 50% of cases, associated with obesity or an increase of 20% of the normal weight;
- daytime sleepiness in 42% of cases;
- agitated sleep in 80% (reported by partner) and disturbed by frequent re-awakenings in 30% of cases;
- difficulties in concentration in 50% of cases;
- loss of memory in 20% of cases and in relation to age (with the exception of pathologies such as Alzheimer);
- ease of falling asleep, including in public places, in 30% of cases;
- alterations in mood and behavior in 5% of cases;
- difficulty to concentrate at work (even if inconsistent) in 30% of cases;
- nocturnal choking sensation in 30% of cases;
- palpitations after nocturnal re-awakenings in 20% of cases;
- morning cephalea in 2% of cases;
- sexual disorders often associated with age; loss of libido, one case (a 45-year-old male).

Physical examination showed obesity in 50% of cases, evaluated according to the BMI, waste/hip ratio, and neck circumference. The risk factors noted were obesity, smoking, and use of sedatives.

After diagnosis, the patients were subjected to further laboratory and instrumental examinations as follows:

- routine examinations (particularly hemochrome, lipid and glucide levels, if necessary);
- spirometry and plethysmography;
- hemogasanalysis if necessary;
- nocturnal monitoring of blood pressure during polysomnographic examination and/or for 24 hours;
- 24-hour Holter ECG recording if necessary;
- nocturnal electroencephalogram and neurological assessment if necessary.

At the same time we continued to treat and monitor the basic conditions.

*Grading*

Severity grade was fixed according to the following parameters: number of apneas in relation to respiratory disturbance index (RDI), body position during nocturnal sleep, time necessary for falling asleep (limits fixed at 400 seconds), oxyhemoglobin saturation values (Simmonds' scale).

*Data*

- *Stage 2:* 73% (RDI from 15 to 30 with severe oxyhemoglobin desaturation often occurring while awake and during physical exercise);
- *Stage 3:* 27% (RDI > 30, patients with severe alterations until they experience cardiorespiratory failure).

OSAS was the most frequent nocturnal apnea syndrome, often seen with mixed patterns in the central apnea. Severe cases were treated with combined therapy (oxygen plus BiLEVEL-PAP), 73% of cases with BiLevel-PAP only.

If necessary, it was suggested that the patients should avoid the use of alcohol, hypnotics, and sedatives, as well as supine decubitus.

## Results

After six months of therapy, control monitoring was carried out (polysomnography, respiratory pressure control). In order to evaluate the response, we collected and subdivided the data into qualitative and quantitative:

- There was a remarkable reduction in the apnea/hypopnea index in 70% of cases with improvement in the cardiorespiratory pattern, *i.e.*, a median reduction of about 50% in the number and type of desaturations in the awake state as well, stabilization of the nocturnal ECG pattern, reduction of hematocrit, an increase of FEV1, and an increase in the number of REM phases in most cases;
- Improvement in cognitive ability, psychological functionality, quality of life, and reduction up to disappearance of snoring.

The most important factor associated with compliance was the significant

improvement in symptomatology. Side-effects were more frequent in patients who did not comply with the therapy.

Twenty-five percent of patients abandoned the therapy during the first two to four weeks, while the remaining 75% continued the treatment in a rather consistent manner (five days a week for about six hours a night, on average). Moreover, reduced compliance occurred in relation to difficulties in adapting to the pressure, only 2% of patients complained about difficulties in adapting to the mask and 5% to the ventilator, either because of its dimensions or because it was too noisy.

We noted an improvement in airway morphology, leading to a remarkable improvement in the patients' general situation, which was particularly important in those cases with concomitant pathologies.

Since these are not urgent at the moment, no otorhinolaryngological treatments were carried out during the present study. A second control will be performed after the next polysomnographic monitoring.

Even in a limited way, our study shows that it is possible to approach this complex pathology starting with evaluation of the general clinical condition of the patient, never forgetting the huge experience of otologists in this field.

The use of positive-pressure ventilators should also observe these considerations, never forgetting that a COPD patient's treatment requires thorough and continuous monitoring for the following severe side-effects: pulmonary hypertension, respiratory insufficiency, and chronic cor pulmonale.

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# IMPACT OF A PRESSURE RAMP ON COMPLIANCE WITH CONTINUOUS POSITIVE AIRWAY PRESSURE THERAPY FOR SLEEP APNEA/HYPOPNEA*

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Continuous positive airway pressure (CPAP) is the medical therapy of choice for obstructive sleep apnea/hypopnea (OSA/H), but sub-optimal compliance is the greatest limitation of this modality. Pressure ramping provides a 'window' of time during which the patient receives less than the therapeutic level of pressure, and may provide an enhanced opportunity to fall asleep.
*Hypothesis:* Routine prescription of a pressure ramp does not improve compliance with CPAP therapy in OSA/H patients.
*Study design:* Retrospective chart review.
*Patients:* Patients with OSA/H by full-night polysomnography and who had full-night CPAP titration with the prescription of CPAP between January and December 1996; 113 patients (81 male, 32 female). Some physicians at the authors' center routinely prescribe ramp or humidification (pass-over humidifier), others do not. Seventy-six patients were prescribed CPAP with ramp (ramp group) and 37 patients were not (no ramp group); a humidifier was also prescribed in 93% of patients in the ramp group, and in 68% patients in the non-ramp group.
*Analysis:* Unpaired *t* test. Data reported as mean ± SE.
*Results:* The results are detailed in Table 1.

*Table 1.*

| | *No ramp* | *Ramp* | *p value* |
|---|---|---|---|
| Age, years | 48.32 ± 2.1 | 49.37 ± 1.5 | 0.69 |
| Body mass index, kg/m$^2$ | 35.61 ± 1 | 37.2 ± 1.2 | 0.4 |
| Baseline Epworth score | 12.06 ± 0.9 ($n$ = 36) | 11.87 ± 0.8 ($n$ = 74) | 0.88 |
| Baseline AHI | 41.28 ± 5.9 | 49.92 ± 3.7 | 0.2 |
| Baseline desaturation frequency | 20.23 ± 5.8 | 23.21 ± 3.4 | 0.64 |
| Baseline arousal index | 32.52 ± 4.2 | 34.92 ± 2.7 | 0.62 |
| CPAP, cm $H_2O$ | 9.85 ± 0.6 | 11.74 ± 0.4 | 0.01 |
| AHI on CPAP | 5.75 ± 0.8 | 8.77 ± 1.3 | 0.11 |
| Desaturation frequency on CPAP | 0.57 ± 0.2 | 1.19 ± 0.4 | 0.34 |

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| | | | |
|---|---|---|---|
| Arousal index on CPAP | 8.15 ± 0.8 | 11.41 ± 1 | 0.03 |
| Days until meter-read | 44.14 ± 3.8 | 54.53 ± 3.9 | 0.1 |
| Compliance (average CPAP-run time/day, hours) | 4.31 ± 0.4 | 4.01 ± 0.3 | 0.56 |

*Conclusions:* Differences in CPAP level and arousal indices on CPAP are not likely to be clinically significant influences on compliance. Although the impact of humidification requires further study, it appears that routine prescription of ramp does not enhance compliance with CPAP therapy for OSA/H.

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# IMPACT OF NON-INVASIVE NOCTURNAL POSITIVE PRESSURE VENTILATION ON SLEEP AND ARTERIAL BLOOD GASES*

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## Abstract

Non-invasive nocturnal positive pressure ventilation (NIPPV) is increasingly applied in treating patients with neuromuscular/chest wall disorders (NMD/CW). The authors conducted a review of the literature and their own experience in order to assess the impact of abnormal breathing during sleep on sleep quality, and to examine the relationship between NIPPV-related changes in nocturnal arterial blood gases (ABGs) and changes in awake ABGs. Sleep complaints are common in NMD/CW patients. Post-polio patients with ventilatory muscle involvement have decreased total sleep time and sleep efficiency (SE) compared with post-polio patients with isolated limb or bulbar involvement. Post-polio patients without pulmonary involvement have normal SE and architecture. NIPPV improves SE and decreases arousal frequency in post-polio patients, as well as in patients with myopathies, dystrophies, and myasthenia gravis who have non-obstructive sleep-disordered breathing. Withdrawal of NIPPV results in reduced sleep continuity, which is unrelated to apneas or hypopneas but which may be related to oxyhemoglobin desaturation and hypercapnia.

NIPPV reduces awake arterial carbon dioxide tension ($PCO_2$) in hypercapnic NMD/CW patients. The mechanism is not well defined, and it is not known whether reduction of $PCO_2$ during sleep is important for a successful therapeutic outcome. The authors speculated that if NIPPV did not reduce nocturnal $PCO_2$ in patients who experienced a reduction in awake $PCO_2$, this would provide evidence against the importance of improving ABGs during sleep. To address this issue, they reviewed three published data sets in which awake ABGs and nocturnal $PCO_2$ ($PaCO_2$, arterial, measured in one study, and $PtcCO_2$, transcutaneous, monitored in two), as well as their own clinical data, including $PaCO_2$ during wakefulness and sleep. In all studies, nocturnal $PCO_2$ was reduced on NIPPV compared with sleep without NIPPV. In addition, $PCO_2$ during wakefulness was reduced during the period of NIPPV compared with the period when NIPPV was not employed during sleep. In all four studies, there was a notable similarity between the average $PCO_2$ during sleep on NIPPV and the average awake $PCO_2$. However, in the authors' data set of seven patients, reduction of $PaCO_2$ during sleep was not invariably associated with a comparable reduction in $PaCO_2$ during wakefulness. In part, this may be due to deterioration of pulmonary function due to NMD/CW in some patients during the follow-up interval.

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*Conclusions:* NIPPV improves sleep efficiency and continuity in patients with NMD/CW. Although ventilatory assistance during sleep in hypercapnic patients is clearly of benefit, the importance of reducing $PCO_2$ during sleep in order to normalize $PCO_2$ during wakefulness with NMD/CW remains unclear.

# AUTO-ADJUSTED CONTINUOUS POSITIVE AIRWAY PRESSURE IN THE TREATMENT OF SLEEP APNEA/ HYPOPNEA SYNDROME*

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Sleep apnea/hypopnea syndrome (SAHS) is an important public health problem associated with a serious increase in the morbidity rate related to cardiovascular and cerebrovascular diseases and to neuropsychological dysfunction. SAHS is also associated with increased mortality. This increase in risk factors emphasizes the need for an effective treatment. The usefulness of nasal continuous positive airway pressure (CPAP) in the treatment of SAHS was first reported by Sullivan *et al.* in 1981,[1] and it is still considered to be one of the most effective forms of treatment since it is associated with an improvement in morbidity and mortality. However, the regular use of CPAP is associated with numerous side-effects related to nasal airflow and pressure discomfort that condition its acceptance.

The effective positive pressure level (Peff) which generally corresponds to the level of pressure that gets rid of apnea, hypopnea and snoring, in all sleep stages and for all body positions, may vary according to different clinical situations, such as alcohol and sedative medication intake, and changes in body position. Peff level is also influenced by sleep stages, upper airway collapsibility being higher in stages I-II and REM than in slow wave sleep, and studies demonstrated that Peff progressively decreases during the course of CPAP therapy. This suggests that the positive pressure requirements may change during one night, and from one night to another on a short- and long-term basis. This has led to the development of new positive pressure devices that continuously adjust the positive pressure level during the night (auto CPAP), allowing a decrease in the pressure level when apnea/hypopnea disappear, and an increase in this pressure level when the sleep respiratory disorders reappear. These devices are still being investigated in order to confirm their efficacy in SAHS treatment, and to assess the absence of complications related to their mode of action, such as: (1) recurrence of sleep fragmentation according to repetitive changes in the positive pressure level; (2) lack of efficacy and recurrence of apnea or hypopnea when the positive pressure level is low.

Several autoCPAP devices have been developed that perform in different ways. AutoCPAP Morphée plus (Nellcor Puritan Bennett) is characterized by its ability to adapt the level of pressure applied during the night within a determined pressure range (+2 $cmH_2O$ and -4 cm $H_2O$, respectively, around a predetermined Peff). This pressure adaptation is regulated by a constant feedback analysis of the patient's ventilation by the nasal CPAP device, according to the flow regimen provided by the CPAP compressor. Its efficacy has been confirmed during one polysomnographic night[2] and after three weeks of home treatment, on the regression of sleep-related breathing disorders, as well as on the normalization of daytime vigilance.[3] Its

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regular use was associated with a significant reduction in the mean level of pressure during slow-wave sleep and a significant improvement in daily compliance.

AutoCPAP REM plus autofunctioning is based on the detection of apnea from a pressure transducer, and on snoring detection according to the analysis of acoustic vibrations (Nellcor Puritan Bennett). This device allows positive pressure changes within predetermined limits around Peff, and its efficacy has been confirmed during a polysomnographic night on the regression of sleep respiratory disorders.[4] Its use was associated with a significant reduction in the mean level of positive pressure during the night. Its efficacy on hypopnea has recently been improved, and its mode of action is still under evolution and looks promising.

AutoCPAP Virtuoso (Respironics) and AutoCPAP Horizon (DeVilbiss) detect airflow instability according to vibration recording in the upper airways. These devices are characterized by the ability to allow positive pressure changes within large limits, without any predetermination of Peff. As a consequence, they can first be used as auto-titrating systems, and then as autoCPAP systems. The efficacy of the Respironics prototype has been confirmed in the autoCPAP mode during a polysomnographic night associated with a significant reduction of mean positive pressure during the night compared to manually determined Peff.[5] In a recent study performed with the DeVilbiss device, the substitution of automatic CPAP titration instead of a manual titration in patients with SAHS did not reduce the numbers accepting the treatment at six weeks.[6]

AutoCPAP Autoset (ResMed) functioning is based on the simultaneous detection of apnea, snoring, and flow-limited respiratory cycles, by analyzing the curve of inspiratory airflow against time. This system was the first to be used as a diagnostic method.[7] Furthermore, its efficacy has been demonstrated in the auto-titration mode when compared to manual titration during two successive polysomnographic nights.[8]

However, further studies are still needed in order to assess the long-term efficacy of these autoCPAP, and to discover whether their regular use could be associated with better tolerance and compliance, as was initially proposed. Furthermore, these studies should allow better characterization of the precise indications for such devices.

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# MISCELLANEA

# A COST BENEFIT ANALYSIS OF OBSTRUCTIVE SLEEP APNEA SYNDROME

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Clinical trials for obstructive sleep apnea syndrome (OSAS) are analyzed from an economic point of view, with the aid of data provided by the hospital economic management. The analysis attempts to give an idea of which are the best clinical trials for OSAS in adult patients. We used both diagnostic trials and the costs to patients and hospitals.

The diagnosis of OSAS is made as quickly as possible in order to reduce the possibility of various complications.

The cost and time necessary for a visit or for a number of examinations in both public hospitals and private clinics are analyzed by comparing the different types of analysis. Diagnosis in a hospital is less expensive than in a private clinic, but the waiting time is less in the private sector. Nowadays, the only place where examinations to diagnose OSAS can be carried out is in a consulting room, because the health system does not provide a diagnostic procedure or admission to hospital.

In cases of OSAS, with the help of the specialist, the patient can choose from three types of treatment. If he chooses the first type, the patient will receive different treatments according to the various causes of OSAS. Therefore, it is difficult to analyze the cost and time of this kind of treatment.

The second choice is mechanical therapy with continuous positive airway pressure (CPAP), nasal CPAP, or auto CPAP. In this case, the patient can rent the CPAP instrument for between 200 and 300,000 lire per month up to a total cost of 2,5000,000 lire, or he can buy it outright. The second alternative, *i.e.*, about 3-3,5000,000 lire, will be more suitable if the therapy will last for more than a year.

The third choice is surgery. In this case the patient can make use of a public or a private facility, but there is a great difference in the cost and time of execution of the treatment.

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We analyzed different types of surgical procedure, such as septoplasty, laser-assisted uvulopalatoplasty (LAUP), uvulopalatoplasty, uvulopalatal flap, advance of the tongue base, adenotonsillectomy, and the radiofrequency procedure. In each case, we analyzed the cost, including surgeon, nurse, non-medical staff, drugs, operating room, laboratory, radiology, and costs deriving from other services.

We compared the medium-specific cost with the disease-related groups (DRG) reimbursement system, and noted that the normal procedure with a minimum of two nights in hospital is not economical for septoplasty, adenotonsillectomy or advance of the base tongue. However, it is impossible to carry out these procedures in any other scenario, due to the possibility of postoperative complications (see the clinical trials suggested by the Italian Otorhinolaryngology Society, SIO).

In conclusion, LAUP is the only procedure that can be executed on an outpatient basis, with the possibility of staying one night in hospital in case of complications (day surgery).

On the other hand, the only place where the radiofrequency procedure, nowadays too expensive for public hospitals, can be carried out is a private clinic with no insurance reimbursement.

After the cost benefit analysis of OSAS clinical trials, we can conclude that the best way to reach a quick and low-cost diagnosis of OSAS, is a day/night procedure; in fact, this procedure allows hospitals to compete with private clinics with regard to time of diagnosis. At the same time, the patient has the possibility of a high standard of efficiency at a cost that is certainly lower than the private sector.

# OBSTRUCTIVE SLEEP APNEA TREATMENT IN A GENERAL ENT PRACTICE IN THE NETHERLANDS

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Since the first presentation of obstructive sleep apnea syndrome (OSAS) treatment by Ikematsu at the World Congres in Miami 1978, we have been carrying out so-called classical uvulopharyngoplasty (UPP) procedures since 1979. For more than 20 years, the number of UPP interventions for OSAS has remained more or less constant, amounting to between ten and fifteen per year.

In 1995 we introduced laser-assisted uvuloplasty (LAUP), carried out as an outpatient procedure under local anesthesia. The number of LAUP interventions increased from 16 in 1995 to 28 in 1998. With the introduction of LAUP, there was an overall decrease in the number of classical UPP operations.

In January 1999 we began using radiofrequency (RF) treatment for OSAS and the number of cases using this technique increased markedly to 42, while the number of cases being treated with LAUP dropped to 12 annually. The number of cases being treated by UPP remained constant. These changes can be explained by the milder morbidity of RF treatment compared to LAUP, as well that, when LAUP treatment is unsuccesful, RF is still an option.

The overall increase in interventions for OSAS is due to the recent general awareness that snoring is a social problem.

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# SNORING AND SLEEP APNEA/HYPOPNEA SYNDROME

## A survey of the effects of an informative campaign on a resident population*

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**Aim**: The authors evaluated the motivation and geographical provenance of patients who presented at the Division of Respiratory Rehabilitation of Sondrio Hospital in 1998 for sleep breathing disorders after informative and advertising campaigns, with the aim of evaluating to what extent such an informative campaign alerts physicians and the population to these problems.
**Methods:** In 1997, the authors led an informative local campaign by meeting with general practitioners and specialists, and by advertising via newspapers and TV. During 1998, they examined those persons who presented at their service by means of a questionnaire, screening polysomnography and a sleep diary.
**Results:** In 1998, the authors examined 146 patients (80% males aged 28–74 years versus 20% females aged 60–70 years). Eighty percent of these persons presented with obesity, 70% with hypertension, 60% with COPD, and 5% with other pathologies, especially endocrine and metabolic disorders. With regard to snoring and sleep apnea/hypopnea syndrome (SAHS), of the persons examined, snoring only was seen in 10%, mild SAHS in 10%, moderate SAHS in 50%, and severe SAHS and overlap syndrome in 30%. Fifty percent of the patients were resident in Valtellina. The patients presented to our service with the following motivations: 5% wanted a valuation of their daytime sleepiness; 60% were spurred on by their partners; 34.9% were referred by others specialists, and just 0.1% by their general practitioner. During 1998, there was no statistical difference in the access data to our center, compared to 1997.
**Conclusions:** Despite the fact that patients with sleep breathing disorders consult their doctor for a variety of other medical problems (Ohanyon *et al.* British Medical Journal 314:860-863, 1997), they are unlikely to be investigated by their doctor. It is nearly always the fact that their partner is irritated by their snoring that induces the patient to consult a specialist at a sleep center. Despite the epidemiological and medical importance of SAHS, both doctors and patients prefer to sleep rather than stay awake over it.

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