SLEEP APNEA

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MEDICAL GRAND ROUNDS

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"What did it matter where you lay once you were dead? In a dirty sump or in a marble tower on top of a high hill? You were dead, you were sleeping the big sleep, you were not bothered by things like that. Oil and water were the same as wind and air to you. You just slept the big sleep, not caring about the nastiness of how you died or where you fell."

The Big Sleep by Raymond Chandler

INTRODUCTION

The French neurologist Gastaut was the first to realize that abnormal breathing at night could result in daytime symptoms and disease (1). Since that time, our understanding of the relationships between sleep, breathing, and illness has advanced considerably, and this review will examine current concepts of a relatively common sleep disorder, the sleep apnea syndrome. There are several reasons why physicians should be aware of sleep apnea. The sleep apnea syndrome is surprisingly common, with the most conservative estimates showing a 1% prevalence in a population of gainfully employed males (2). When severe, sleep apnea causes significant morbidity and mortality which is preventable, since effective therapy exists. Thus, early diagnosis and treatment of sleep apnea syndrome is a desirable goal.

In addition to reviewing sleep apnea's clinical features this protocol will emphasize the cardiovascular consequences of sleep apnea, the pathogenesis of upper airway obstruction, screening tests for sleep apnea, and selection of appropriate treatment for individual patients. Most of the material to be presented deals with sleep apnea syndrome caused by upper airway obstruction (obstructive sleep apnea or OSA), since OSA is by far the commonest type of sleep apnea and most investigations have been performed with OSA patients or animal models of OSA.

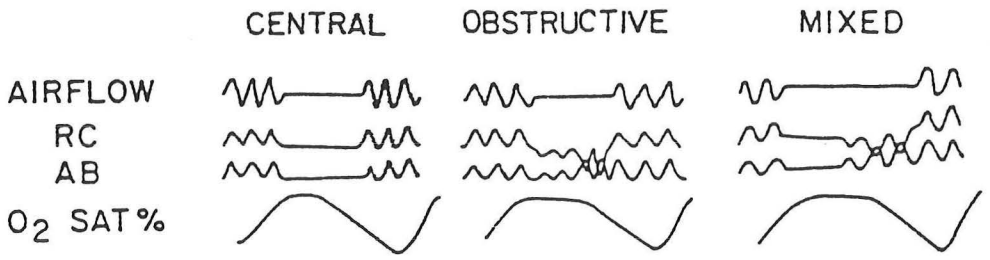
DEFINITIONS

APNEA refers to ≥ ten seconds of zero airflow, usually measured at the nose.

APNEA INDEX (AI) is the average number of apneas/hr measured during an overnight sleep study.

Figure 1

THREE TYPES OF SLEEP APNEA



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SLEEP APNEA SYNDROME is symptomatic sleep apnea. Most investigators require that at least five apneas/hr be present to diagnose sleep apnea syndrome, since fewer than five apneas/hr are not thought to be clinically significant (3,4). There are three types of sleep apnea - obstructive, central, and mixed.

OBSTRUCTIVE SLEEP APNEA (OSA) occurs when upper airway obstruction develops during inspiration. The diaphragm and other inspiratory muscles continue to contract, and thus abdominal and rib cage movement is evident during the apnea (Figure 1, middle panel). OSA is the commonest cause of sleep apnea syndrome.

CENTRAL SLEEP APNEA occurs due to failure of inspiratory muscle activation. No rib cage or abdominal movement occurs during apneic episodes (Figure 1, left panel). Pure central sleep apneas are exceedingly rare.

MIXED SLEEP APNEA begins as a central sleep apnea but soon inspiratory muscle effort becomes obvious (Figure 1, right panel). Most patients with OSA also have mixed apneas, and mixed apneas improve with therapies which prevent OSA. Thus, it is

clinically useful to consider mixed apneas and OSA as the same disorder.

DESATURATION indicates ≥4% fall in hemoglobin oxygen saturation from a stable baseline saturation level.

HYPOPNEA means some arbitrary decrease in airflow (usually >25%) accompanied by a >2% fall in oxygen saturation.

OBESITY HYPOVENTILATION SYNDROME (OHS) refers to patients with OSA who are obese and have a chronic respiratory acidosis (daytime $PaCO_2$ > 45 mmHg). The Pickwickian Syndrome is synonymous with OHS.

CLINICAL PRESENTATION OF SLEEP APNEA SYNDROME

Most (>90%) OSA patients are male. The average age of males at diagnosis is 45, with a range from 25 to 60 years (5,6). OSA can occur in post-menopausal females but is almost never seen in younger women. It is likely that both low testosterone and high progesterone levels protect females from OSA. Testosterone has been shown to cause OSA and progesterone stimulates respiration and has been used with some success to treat OSA (7-9). Most (85%) OSA patients present to physicians with a chief complaint of daytime somnolence. Other common OSA symptoms are listed on Table 1.

Table 1

COMMON OSA SYMPTOMS

SYMPTOM	FREQUENCY (%)
NOISY SNORING/SNORTING	100
ABNORMAL SLEEP MOVEMENTS	100
EXCESSIVE DAYTIME SLEEPINESS	85
PERSONALITY CHANGE	65
INTELLECTUAL DETERIORATION	60
AUTOMOBILE ACCIDENT(S)	66
IMPOTENCE	50
MORNING HEADACHE	45
HYPNAGOGIC HALLUCINATIONS	40

When taking a history from a patient with possible OSA it is very informative to question the patients' bedpartner, since only the bedmate can describe the patients snoring and sleep movements. Most OSA patients are lifelong snorers. OSA patients snore with a characteristic sequence of loud snores followed by silence (the apnea) followed by loud snorting noises as airflow resumes. Normal snoring, which is present in 30-40% of adult males, is more regular and is not interrupted by silent periods or

snorting. Abrupt, forceful movements of the extremities are common, can injure the patients' bed partner, and frequently (40% of spouses) cause the bed partner to seek safety in a separate bed.

Pathological degrees of daytime sleepiness are present in 85%. Somnolence can be quantitated by the multiple sleep latency test, which measures the time required for subjects to fall asleep during daytime naps. OSA patients fall asleep so rapidly that their sleep latency time is usually <5 minutes (10). The severe somnolence leads to poor work performance, frequent unemployment, and an alarming proclivity for automobile accidents caused by falling asleep at the wheel. In one series, 41% of OSA patients had at least one accident in the preceding five years, and many had more than one crash (11). Daytime sleepiness is caused by chronic sleep deprivation. As will be reviewed, OSA patients spend little time in deep (stage 3 or 4) sleep, have fragmented REM sleep, and have frequent arousals to wakefulness. About 50% of patients report impotence, morning headaches, and daytime hallucinations. The latter are called hypnagogic hallucinations because they occur while patients are falling asleep during the day.

Other than being overweight, most OSA patients have unremarkable physical examinations. Table 2 lists the presenting signs of OSA.

Table 2

SIGNS OF OSA

SIGN	FREQUENCY (%)
OBESITY	70
SYSTEMIC HYPERTENSION	40-60
OBESITY HYPOVENTILATION (OHS)	10-50
ANATOMIC ENT ABNORMALITIES	<5

Obesity, usually defined as a body weight > 120% of ideal weight, is often present, but clearly many normal weight individuals have OSA. Several large series of OSA patients have found that about half have hypertension (12). Conversely, one investigator has screened Veterans Administration hypertension clinic patients for OSA and reported that 30% of hypertensive patients had OSA (13). Few of the patients in this study were symptomatic from OSA. These results have not been confirmed but the suggestion is that clinically occult OSA, manifest only as essential hypertension, is very common. Other investigators have used stepwise logistic regression analysis to determine the relationship of OSA and hypertension and have found that age and obesity account for the

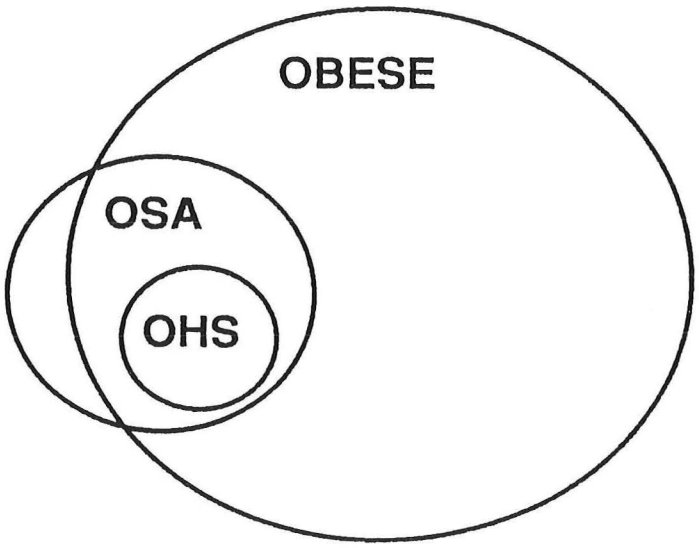
prevalence of hypertension in OSA patients, with OSA per se being of little importance (14).

Fewer than 50% of OSA patients will develop the obesity hypoventilation (OHS) syndrome. These patients are frequently markedly obese, very somnolent, and the diagnosis is made by obtaining an arterial blood gas while the patient is awake; OHS patients have a chronic respiratory acidosis (15). OHS patients

frequently develop cor pulmonale, manifest by peripheral edema, jugular venous distention, a right sided S3 gallop, tricupsid regurgitation, and polycythemia. All OHS patients also have OSA, but the converse is not true; the interrelationships of obesity, OSA, and OHS are shown diagrammatically on Figure 2. It is not known why some OSA patients develop OHS and others do not, although there is some evidence that OHS patients have lower hypoxic and hypercapnic ventilatory drives (16-19).

Figure 2

RELATIONSHIP OF OBESITY TO OSA AND OHS

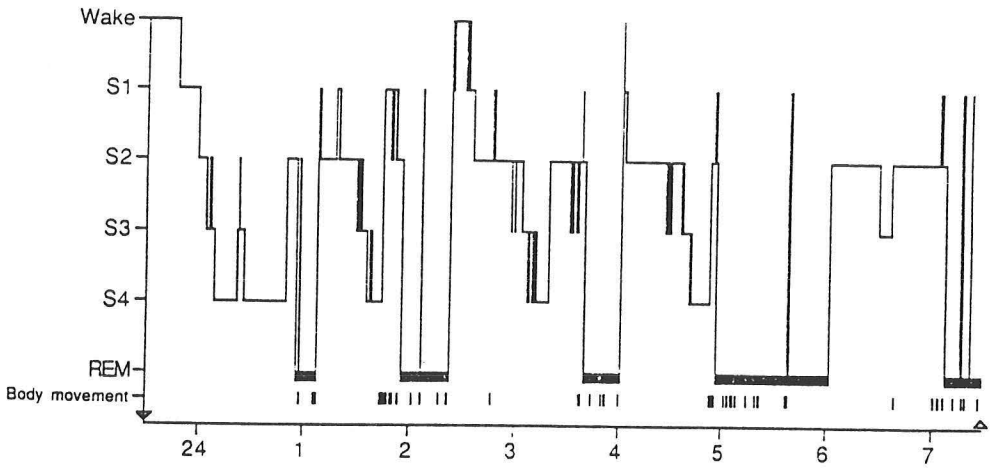


Although most adult OSA patients have smaller upper airway cross-sectional areas than normal people, gross anatomic anomalies of the nose, mouth, and face are unusual (20-21). However, it is important to carefully examine OSA patients for these defects, because surgical repair is usually simple and will cure OSA. Some of the anatomic problems causing OSA include large uvulas, redundant pharyngeal mucosa, enlarged tonsils, nasal obstruction due to polyps or septal deviation, macroglossia, and micrognathia.

NORMAL SLEEP

Figure 3

NORMAL SLEEP ARCHITECTURE



In: Principles and Practice of Sleep Medicine, Chapter 1, p. 3, 1989

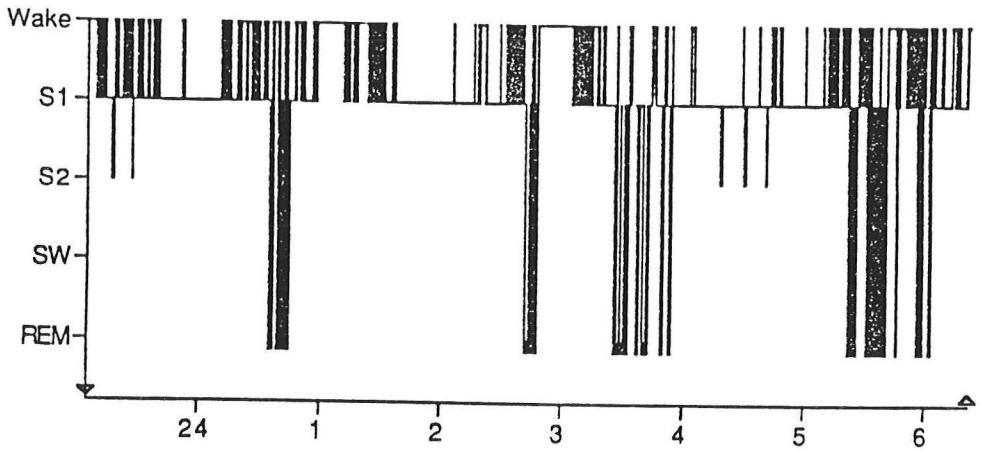
Prior to describing sleep in OSA, the events of normal sleep must be understood. Normal sleep is a cyclical phenomenon in which the sleeper progresses from wakefulness into light sleep (Stages 1 and 2 non REM, or NREM, sleep), slow wave sleep (Stages 3 and 4 NREM sleep), and then REM (rapid eye movement) sleep. The cycle repeats about six times each night (Figure 3). Arousals into wakefulness do occur normally but are infrequent and wakefulness accounts for less than 5% of total sleep time. The normal distribution of sleep time is as follows: Stage 1 (2-5%), Stage 2 (45-55%), Stage 3 (3-8%), Stage 4 (10-15%), and REM (20-25%). Ventilation during NREM sleep is largely regulated by the $PaCO_2$. The medullary chemoreceptor which regulates ventilation becomes less sensitive to CO_2 during Stage 1 sleep, and thus $PaCO_2$ normally rises 3-7 mmHg during sleep (22). Apneas may occur in normal people at the beginning of Stage 1 sleep and during REM sleep. Stage 1 apneas are thought to be due to the decreased sensitivity of the medullary CO_2 chemoreceptor, which causes a temporary cessation of ventilatory drive until $PaCO_2$ increases sufficiently to stimulate a breath (23,24). In contrast to pathologic apneas, normal apneas are short (<15 seconds),

infrequent, and do not cause significant hypoxemia. Studies of asymptomatic adult males have shown that apnea frequency increases directly with age and weight, and up to 70% of healthy males >60 years old have >5 apneas/hr (4,8). Apneas are unusual in healthy premenopausal females but do occur in asymptomatic postmenopausal women (9).

SLEEP IN OSA PATIENTS

Figure 4

SLEEP ARCHITECTURE OF OSA

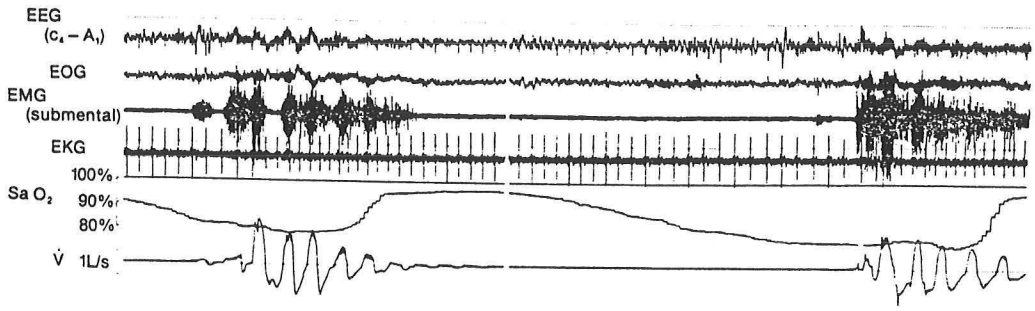


In: Principles and Practice of Sleep Medicine, Chapter 1, p. 3, 1989

Sleep architecture is grossly disrupted in OSA. As shown on Figure 4, patients constantly awaken from Stage 1 sleep and occasionally go directly from wakefulness to REM sleep. Little time is spent in Stage 1 or REM sleep before awakening and virtually no time is spent in Stage 2,3, or 4 sleep. Although the total amount of REM sleep time is normal, the REM sleep that occurs is of short duration due to frequent arousals. Thus, because of a paucity of deep sleep and fragmented REM sleep, OSA patients have poor sleep quality and are chronically sleep deprived. The daytime somnolence of OSA patients is due to a deep sleep deficiency.

Figure 5

POLYSOMNOGRAPHIC RECORDING OF OSA



In: Principles and Practice of Sleep Medicine, Chapter 56, p. 525, 1989

Figure 5 shows a typical polysomnographic recording obtained from an OSA patient during an overnight sleep study and illustrates the relationship of obstructive apneas to sleep and arousal. The recording starts while the patient is apneic, as shown by zero airflow on the bottom tracing ($\dot{V}$ L/S). Not shown are inspiratory muscle efforts, which are present throughout an obstructive apnea and intensify with time. Note the fall in oxygen saturation (SaO_2). Arterial oxygen levels decline rapidly during apneas and desaturations to levels of 40% or less are not uncommon. $PaCO_2$ rises during an apnea, but the increase in $PaCO_2$ is much less than the fall in PaO_2 due to the larger body stores of carbon dioxide, which limit the rate of rise in $PaCO_2$. Eventually the apnea is terminated by an arousal, which is visible on the electroencephalogram as a change to a waking pattern or on a submental electromyogram (EMG) as a burst of activity. To an observer, arousal is evident by a snorting sound as the airway is reopened and often by vigorous movement of the extremities. The exact stimulus for arousal is not know, but it is thought to be due to a combination of strong inspiratory effort against an occluded airway, hypoxemia, and hypercapnia (25,26).

Once awake, patients open their occluded upper airway by activation of pharyngeal muscles such as the genioglossus, which moves the tongue anteriorly. Airflow resumes and the patient falls back into a light sleep. After a variable period of unobstructed breathing, the cycle of obstruction-apnea-arousal repeats itself. Typically, patients with significant OSA will

have between 200 to 500 apneas per night. Apneas usually last >15 seconds and are accompanied by oxygen desaturations of >4% (3).

CARDIOVASCULAR EFFECTS OF OSA

OSA patients develop a number of potentially serious cardiovascular events during sleep (Table 3).

Table 3

CARDIOVASCULAR EFFECTS OF OSA

SYSTEMIC HYPERTENSION
ARRHYTHMIAS
PULMONARY HYPERTENSION/COR PULMONALE

The prevalence of daytime hypertension in OSA patients has already been discussed. Sleep studies performed with invasive hemodynamic monitoring have shown that extreme blood pressure elevations may occur during apneas (Table 4). Hypertension has been attributed to sympathetic nervous system activation due to hypoxemia. Elevated urine and plasma catecholamine levels have been measured in two separate studies (27,28).

Table 4

HEMODYNAMIC CHANGES DURING SLEEP IN SIX OSA PATIENTS

Case No.	Before Tracheostomy			
	Average No. of Apneas per Hour of Sleep	Lowest Recorded Pao_2*	Highest Recorded Pressures†	
			Femoral Artery	Pulmonary Artery
		← *mm Hg* →		
1	78	34	168/100 (123)	38/24 (27)
2	64	50	160/100 (120)	60/40 (47)
3	60	38	205/134 (158)	70/50 (57)
4	63	36	200/120 (147)	80/54 (63)
5	90	30	194/124 (148)	60/48 (52)
6	80	43	170/110 (130)	38/22 (27)
Mean ± SEM	73±5	38±3	(137±6)	(45±6)

Electrocardiographic monitoring during sleep has detected a surprising number of potentially lethal arrhythmias (Table 5).

Table 5

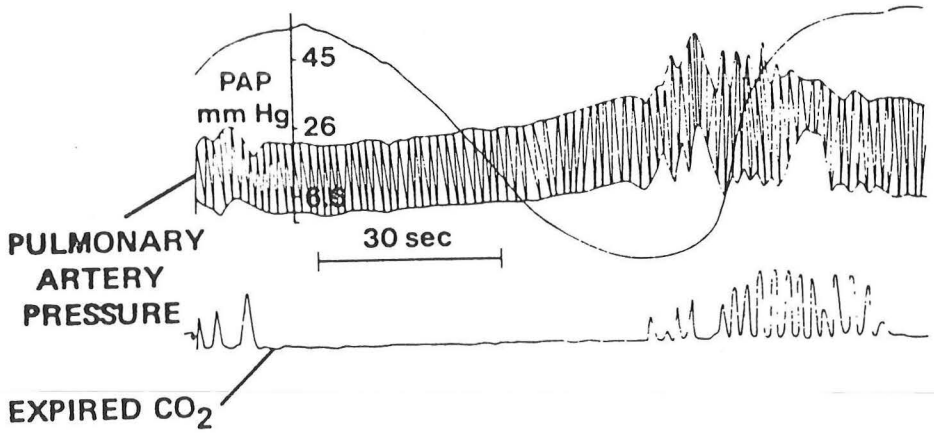
CARDIAC RHYTHM DISTURBANCES DURING SLEEP

RHYTHM	FREQUENCY %
SINUS ARRHYTHMIA	96
SINUS BRADYCARDIA (<30 BEATS/MIN.)	36
ASYTOLE (>20 SECONDS)	36
2ND DEGREE AV BLOCK	16
VENTRICULAR TACHYCARDIA	8
ATRIAL TACHYCARDIA	4

All of the 25 patients in this series had normal baseline, awake electrocardiograms. Arrhythmias and conduction disturbances usually occurred during the second half of an apnea, when the patients were most hypoxemic. Electrocardiographic abnormalities rarely developed unless oxygen saturation was <75% (29). Marked sinus arrhythmia, defined as cyclic variation in the sinus rate of >40 beats/minute, occurs in all OSA patients, and electrocardiographic monitoring to detect sinus arrhythmia has been suggested as a screening test for OSA. The sinus rate falls in direct proportion to apnea duration and hypoxemia. Administration of supplemental oxygen, in sufficient amount to prevent hypoxemia, will prevent sinus arrhythmia (30). Atropine will also prevent it, suggesting that vagal efferents mediate the response. It is interesting that hypoxemic patients are usually tachycardic, but tachycardia in most settings is actually due to a reflex triggered by tachypnea. When hypoxemia occurs in apneic patients, carotid body chemoreceptors cause a vagally-mediated bradycardia (31). Presumably asystole and 2nd degree block are also caused by excessive vagal tone.

Figure 6

EFFECT OF OSA ON PULMONARY ARTERY PRESSURE



Marked hemodynamic changes occur in the pulmonary circulation, as shown on Table 4 and Figure 6. Most awake OSA patients have normal pulmonary artery pressure when measured at rest. During apneic episodes pulmonary arterial pressure rises, frequently to systolic pressures >60 mmHg. After the apnea ends, pulmonary artery pressure falls but often does not drop to the baseline pressure present at sleep onset (32). Thus, repetitive apneas cause both episodic pressure increases and a steadily increasing inter-apnea baseline pressure. A similar phenomenon occurs in dogs exposed to episodic hypoxemia; in the canine model, intermittent hypoxemia is critical for a rising baseline pressure, because continuous hypoxemia does not affect baseline pressure (33).

The episodic apnea-associated rises in pulmonary artery pressure are due to vasoconstriction of small pulmonary arteries caused by alveolar hypoxia. Hypoxic pulmonary vasoconstriction occurs rapidly when alveolar oxygen tension is <60 mmHg and is a basic physiologic response, enabling close matching of perfusion to ventilation by shunting blood blow away from poorly ventilated, hypoxic alveoli (34). The mediator(s) of acute hypoxic vasoconstriction are not known but it is suspected that leukotrienes may be involved. Acute hypoxic vasoconstriction rapidly reverses when normoxia is restored.

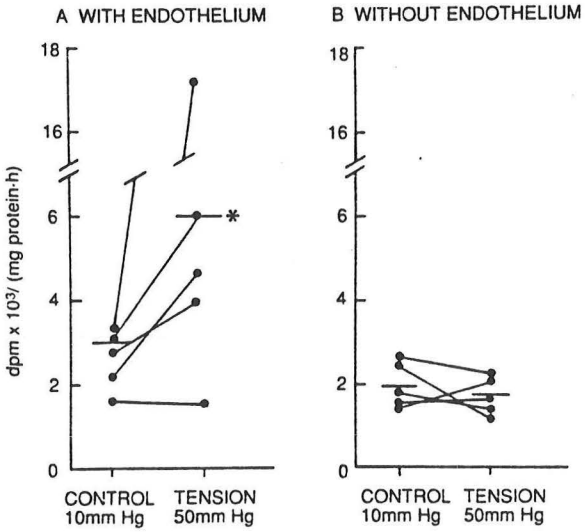
Most OSA patients are normoxic and have normal pulmonary artery pressure while awake, although in one series 20% of OSA subjects had awake pulmonary hypertension (35). When exercised, OSA patients often develop pulmonary hypertension, indicating that the pulmonary vasculature is abnormal. Right ventricular hypertrophy, detected by echocardiography, was present in 70% of OSA patients (36). Cor pulmonale, due to increased pulmonary arterial resistance, develops in a significant number of patients with long standing OSA. Histologic examination of small pulmonary arteries from these patients reveals smooth muscle proliferation and increased amounts of connective tissue. Identical changes have been seen in vessels from chronically hypoxemic COPD patients and are considered pathognomonic of chronic hypoxemia (37). Since most OSA patients are hypoxemic for relatively brief periods of time, it has not been understood how short periods of hypoxemia could cause structural changes in pulmonary vessels and persistent pulmonary hypertension.

Recently, a series of elegant <u>in vitro</u> experiments have elucidated a mechanism by which brief periods of hypoxic vasoconstriction cause structural changes in pulmonary vessels and chronic hypertension. Pulmonary arteries from animals (newborn calves or rats) kept hypoxic for three days were removed, cut into rings, and examined <u>in vitro</u>. Hypoxic pulmonary arteries had an eight fold increased elastin synthesis rate, a 2.5 fold increased rate of collagen synthesis, and had increased levels of pro- 1 (1) collagen MRNA (Figure 7, A).

Aortas from hypoxic animals showed no such changes, suggesting that hypoxia was not the direct cause of increased connective tissue synthesis(38). B-aminopropionitrile, which prevents collagen and elastin fiber formation, significantly reduced pulmonary hypertension in hypoxic animals, an observation suggesting that connective tissue deposition contributes to pulmonary hypertension (39). Further experiments showed that it is pressure, not hypoxia, that stimulates connective tissue systhesis by pulmonary artery rings. As little as four hrs exposure to a modest pressure of 50 mmHg, under normoxic conditions, caused a 35% increase in collagen synthesis, a 110% increase in elastin synthesis, and increased amounts of pro-α 1 collagen MRNA (Figure 7A). Aortic rings subjected to high pressure did not increase connective tissue synthesis. There was also a 71% increase in the level of MRNA for V-SIS, a proto-oncogene coding for a protein homologous to the beta chain of platelet derived growth factor (PDGF) (40).

Figure 7

EFFECT OF PRESSURE ON PULMONARY ARTERIAL ELASTIN SYNTHESIS



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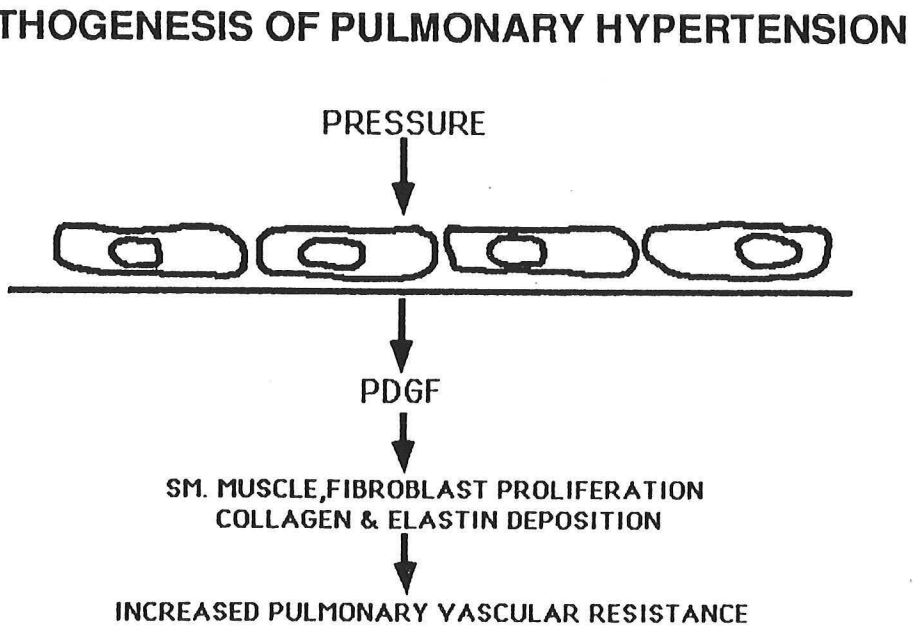
Endothelial cells play a key role in sensing high pressure and signaling to cells present in the media and adventitia. Thus, stripping the endothelium from pulmonary artery rings prior to exposing them to 50 mmHg pressure completely prevented any of the changes described in the above paragraph (Figure 7,B). Cultured human endothelial cells release PDGF and pulmonary arterial cell monolayers exposed to 40 mmHg pressure have increased V-SIS MRNA levels and release a factor which stimulates fibroblast replication (41,42). PDGF, the product of the V-SIS oncogene, stimulates cells via tyrosine kinase activity of the PDGF receptor. PDGF is chemotactic for fibroblasts and smooth muscle

cells, acts as a competence factor for fibroblast and smooth muscle proliferation, and stimulates collagen synthesis (43). These PDGF effects fit all of the observed cellular and biochemical changes seen in hypoxic pulmonary arteries. Transforming growth factor-B (TGF-B) is another putative regulator of pulmonary vessels. TGF-B stimulates fibroblasts to release PDGF and to produce increased amounts of elastin and collagen (44,45). However increased amounts of TGF-B are not present in hypoxic pulmonary arteries (46).

These data suggest the following pathway by which transient hypoxic exposures could cause pulmonary vascular disease (Figure 8). Even brief and modest pulmonary artery pressure elevations, caused by hypoxic vasoconstriction, are enough to stimulate endothelial cells to make and release PDGF (and possibly other mediators). PDGF diffuses into the media and adventitia where it attracts smooth muscle cells and fibroblasts and stimulates them to release collagen and elastin. The net effect of increased cellularity and connective tissue deposition is to transform the pulmonary vasculature from its usual high compliance, low resistance state into a stiff, high resistance circulation. Over time, right ventricular hypertrophy and failure occurs as a result of these changes.

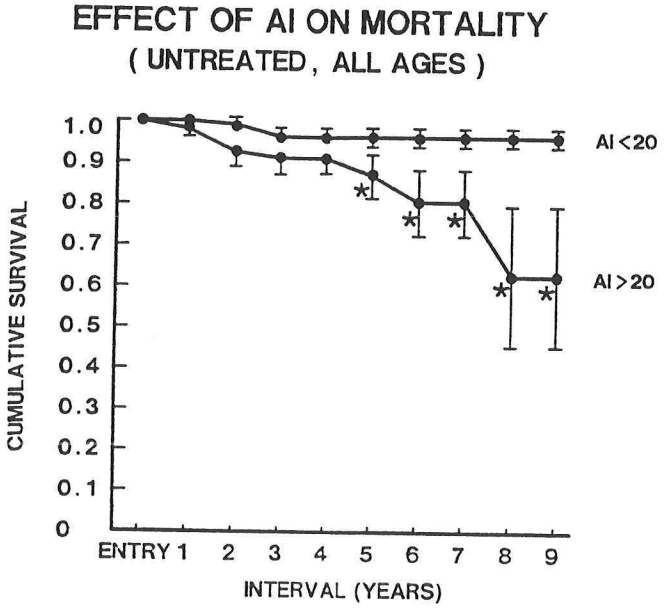
Figure 8



NATURAL HISTORY OF OSA

Recent retrospective evaluations of two large OSA series have revealed that complications and mortality mainly occur in patients with high apnea indexes. In the largest series from Henry Ford Hospital, 385 male OSA patients were followed for 2 to 10 years after diagnosis. 246 received no specific treatment and 118 were treated; 33 patients had a tracheostomy, 25 were treated with continuous positive airway pressure (CPAP), and 60 had uvulopalatopharyngoplasty (UPPP), a surgery which reduces the amount of oropharyngeal soft tissue. For the group of 246 untreated patients, the presence of an apnea index >20/hr was the major predictor of mortality; 11/104 patients with an apnea index >20 died, compared to only three deaths in 142 patients with fewer than 20 apneas/hr (fig 9). By life table analysis, 8 year survival in those with apnea indexes >20 was 63%, versus 96% survival for those with indexes <20. The treated patients were presumably a sicker group, and it was notable that none of the 58 patients treated with tracheostomy or CPAP died, although 8 of the 60 treated with UPPP died. These data suggest that an apnea index >20 identifies high risk OSA patients and that patients with mild disease (apnea index <20) do well without specific therapy (47).

Figure 9



Chest 94:1, 1988

The Stanford University sleep center has followed 198 patients for a minimum of 7 years. 127 patients were treated conservatively with weight loss only, while 71 were treated with a tracheostomy. Patients in the tracheostomy group were sicker, as judged by a higher apnea index at diagnosis (69 $\pm$ 23 versus 43 $\pm$ 31) and more myocardial infarctions. Despite having more severe disease at entry into the study, only 3% of tracheostomy patients were dead at 7 years and only 3% had had a new vascular event (hypertension, stroke, or myocardial infarction). Mortality in the weight loss group (few of whom actually lost weight) was 17% and new vascular events occurred in 12% (48,49). These results confirm that patients with apnea indexes >20 do poorly unless they receive definitive therapy for OSA.

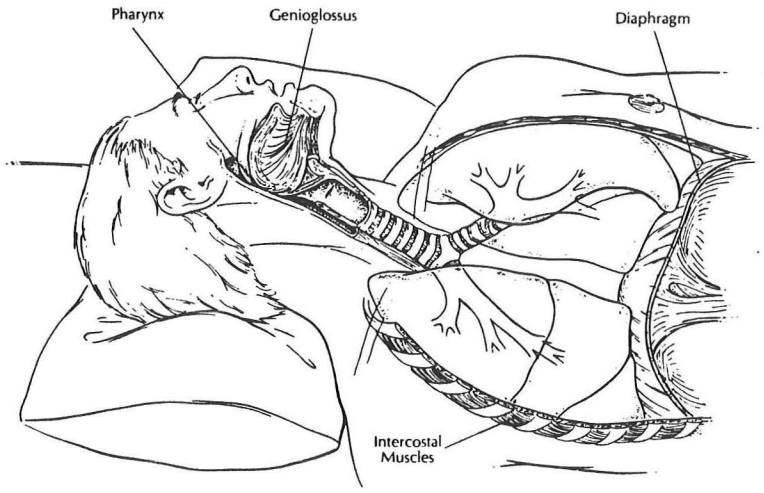
Patients with OHS represent a subset of OSA patients with an extremely high mortality. Neither of the previous two studies separated out OHS patients. However, OHS patients are more often morbidly obese, frequently have right heart failure, and are often admitted to hospital in respiratory failure. One group of investigators has reported that OHS patients have a 70% in-hospital mortality, with about half of the deaths being sudden (50). In summary, both an apnea index >20 and the OHS indicate a poor prognosis for untreated OSA patients.

PATHOGENESIS OF UPPER AIRWAY OBSTRUCTION

The oropharynx, which is the site of obstruction for most OSA patients, differs from other airway segments because it does not have bony or cartilaginous support. Oropharyngeal patency is thus dependant on the co-ordinated action of some 23 pairs of muscles. The genioglossus muscle moves the tongue and normal genioglossal function is particularly important for an open airway, since the tongue forms the entire anterior oropharyngeal border and is freely movable. Figure 10 illustrates the importance of the genioglossus to the oropharyngeal airway. Complete loss of genioglossal tone, as occurs with deep anesthesia or coma, is a well known cause or airway obstruction.

Figure 10

PHARYNGEAL ANATOMY



Hospital Practice 21:81, 1986

Airflow through the upper airway is determined by simple relationships between pressure and resistance. The driving pressure for airflow is the difference between atmospheric pressure at the mouth and nose and the sub-atmospheric pressure generated in the lungs by the diaphragm. Normally the upper airway accounts for 50% of total airway resistance. Increased oropharyngeal resistance not only decreases airflow but also causes airway pressure in the high resistance area to become more negative; this latter effect is critical since the unsupported pharyngeal walls will tend to collapse inward as pressure falls, leading to constantly increasing resistance and more negative pressure until complete occlusion and apnea supervenes.

Table 6 lists the structural and functional oropharngeal abnormalities present in OSA.

TABLE 6

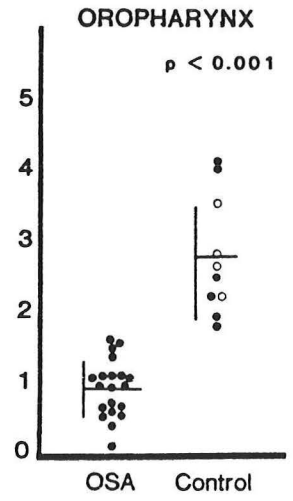
UPPER AIRWAY DEFECTS PRESENT IN OSA

DEFECT	REFERENCE
↓PHARYNGEAL CROSS SECTIONAL AREA	51-56
↑UPPER AIRWAY COLLAPSIBILITY	53,57
↑UPPER AIRWAY RESISTANCE	59,60
↓AND DELAYED GENIOGLOSSAL ACTIVATION	61-63

DECREASED PHARYNGEAL CROSS SECTIONAL AREA - A number of investigators have used either acoustic reflectance or CT scanning to measure upper airway cross sectional areas. Both obese and non-obese OSA patients, studied in the supine position while awake, have smaller naso-, oro-, and hypo-pharyngeal cross sectional areas than either normal weight or obese controls (Figure 11). The oropharynx was consistently the most narrowed segment, and pharyngeal cross sectional area has been shown to correlate inversely with the apnea index (Figure 12). One obese OSA patient lost 68 kg, increased his pharyngeal cross sectional area from 2.7 to 4.1 cm^2, and decreased his apnea index from 117 to 8 (56). It is unlikely that the small pharyngeal areas are due to excess submucosal fat or soft tissue, since no increase in fat density has been noted on CT scans and normal weight OSA patients also have narrowed oropharynxes.

Figure 11

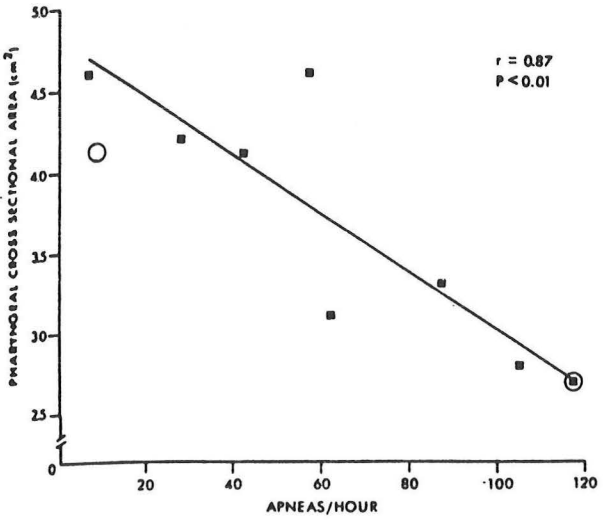
UPPER AIRWAY NARROWING OF OSA



Am. Rev. Respir. Dis. 127:221, 1983

Figure 12

RELATIONSHIP OF APNEA INDEX TO PHARYNGEAL SIZE



Am. Rev. Respir. Dis. 129:355, 1984

There is evidence that oropharyngeal narrowing is secondary to lower lung volumes. OSA patients have significantly smaller lung volumes at functional residual capacity (FRC) and residual volume (RV) than do healthy obese subjects (Table 7).

TABLE 7

PHARYNGEAL SIZE VARIES WITH LUNG VOLUME IN OSA PATIENTS

	SUBJECTS	
	OBESE	OBESE PLUS OSA
WGT (% PREDICTED)	176	209
TLC (% PREDICTED)	106	90
FRC (% PREDICTED)	94	68
RV (% PREDICTED)	116	87
PHARYNGEAL CROSS SECTIONAL AREA (CM^2)		
AT TLC	5.6 ± 0.2	5.0 ± 0.2
AT FRC	4.6 ± 0.4	3.4 ± 0.2
AT RV	3.9 ± 0.3	2.3 ± 0.3

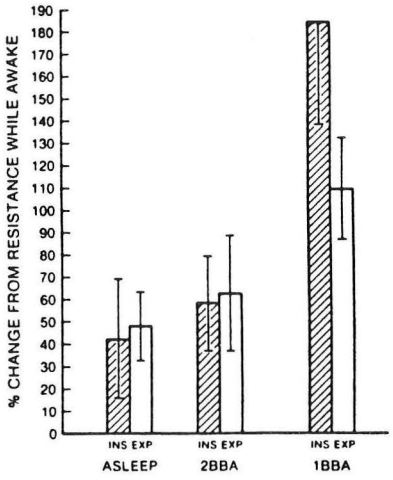
Airway cross sectional area is usually measured at FRC but, when cross sectional area is measured at full inspiration (total lung capacity, TLC), OSA patients and obese controls have similar pharyngeal dimensions (53). The observation that oropharyngeal area of OSA patients varies with lung volume suggests increased collapsibility. Thus, the smaller airway of OSA patients may be due to a combination of decreased FRC and increased collapsibility. Whatever the mechanism, it is clear that OSA patients, even while awake and breathing normally, have a compromised oropharyngeal airway.

INCREASED COLLAPSIBILITY - Two different studies have documented large decreases in oropharyngeal area at low lung volumes, indicating increased collapsibility of pharyngeal walls. Increased collapsibility may explain why apneas are more severe during REM sleep. The intercostal muscles lose tone during REM, causing rib cage instability and a further fall in FRC (58).

INCREASED PHARYNGEAL RESISTANCE - Supraglottic airway resistance, measured awake in the supine position, is 3.5 times higher in OSA patients than in normal controls (60). The increased resistance reflects smaller pharyngeal cross sectional areas. During sleep, inspiratory resistance increases by 180% during the last breath before each apnea (Figure 13). As reviewed previously, high pharyngeal resistance will increase negative pressure in the pharyngeal lumen, promoting further collapse unless pharyngeal muscles are activated and stiffen the pharyngeal wall.

Figure 13

PHARYNGEAL RESISTANCE INCREASES PRIOR TO AN APNEA

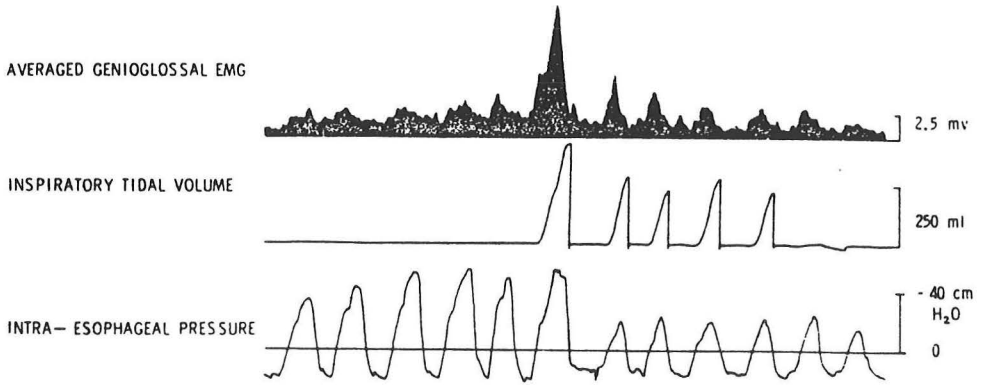


Am. Rev. Respir. Dis. 127:554, 198
1BBA = BREATH BEFORE APNEA

DECREASED/DELAYED GENIOGLOSSAL ACTIVATION - Normally genioglossal activity, as reflected by the genioglossal EMG signal, remains at a high level throughout NREM sleep. Peak genioglossal activity occurs prior to each inspiration. The effect of this normal pre-inspiratory pattern of activation is to stiffen and open the oropharynx, preventing oropharyngeal collapse as negative pressures are generated by the diaphragm. Pharyngeal muscles thus act as important accessory muscles of inspiration (65). A local reflex, capable of sensing negative pressure and increasing genioglossal activity, is important for airway patency in rabits (68). A similar reflex in humans may explain the observation that topical pharyngeal anesthesia provokes OSA in normal subjects (69).

Figure 14

GENIOGLOSSAL ACTIVITY DURING AND AFTER AN APNEA

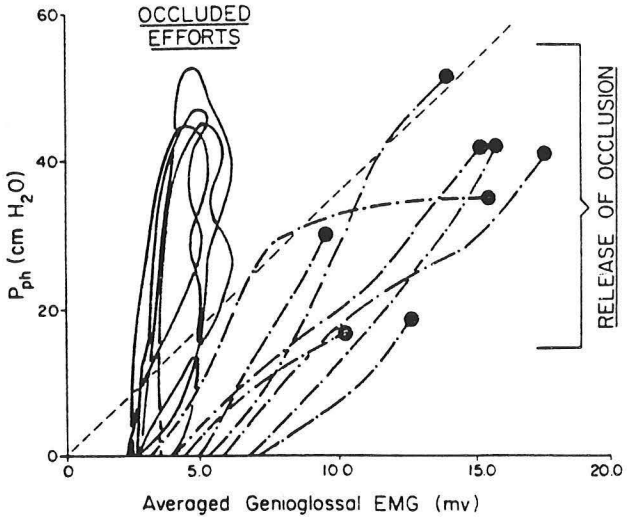


J. Appl. Physiol. 44:931, 1978

Reduced genioglossal activity, which presumably reflects abnormal activation of other upper airway muscles, is a consistent finding in OSA. Genioglossal activity typically falls as OSA patients enter Stage 1 sleep and reaches a nadir at the start of an apnea, while diaphragmatic activity continues at normal levels (Figure 14). During the apnea genioglossal activity remains low; with arousal there is a burst of activity which reopens the airway so that airflow resumes.

Figure 15

PHARYNGEAL PRESSURE AND GENIOGLOSSAL ACTIVITY DURING AND AFTER APNEA



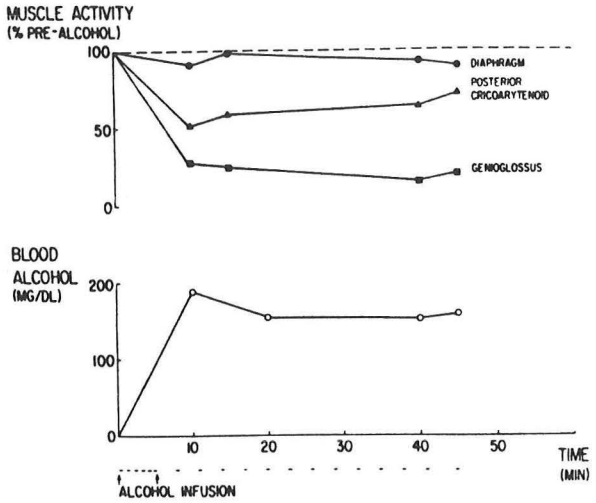
J. Appl. Physiol. 44:931, 1978

Figure 15 shows the relationship of pharyngeal pressure and genioglossal activation. While the genioglossal EMG is at its lowest level, pharyngeal pressure becomes markedly negative and the oropharynx collapses. Airway opening occurs due to muscle activation, shown by a two to three fold increased EMG signal. In addition to reduced activity, asynchrony between genioglossal and diaphragmatic activation has been observed as well. When OSA patients sleep, genioglossal activation precedes diaphragm activation during 90% of normal breaths. During 86% of occluded breaths diaphragmatic activation preceded genioglossal activation (63). The failure of normal upper airway muscle activation is probably the key event in OSA and explains the increased resistance and collapsibility noted previously.

Additional evidence supporting a critical role for reduced genioglossal activation comes from experiments with alcohol. In cats, moderate blood alcohol levels cause a selective depression of upper airway motor neuron activity but have no effect on phrenic nerve activation (Figure 16) (70).

Figure 16

SELECTIVE EFFECT OF ALCOHOL ON THE GENIOGLOSSUS



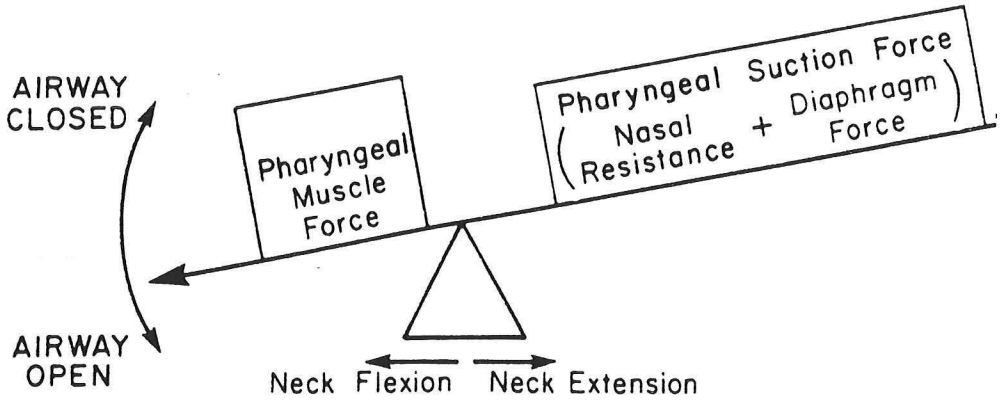
Am. Rev. Respir. Dis. 130:156, 1984

Administration of alcohol prior to sleep induces apneas in normal subjects and markedly increases the number of apneas in OSA patients (71,72). Why OSA patients have decreased upper airway muscle activation is unknown. Some patients may be genetically predisposed to reduced genioglossal activation (73). Respiratory drive, as measured by ventilatory and diapragmatic EMG response to carbon dioxide, or by the ventilatory response to hypoxia, is decreased in OSA patients, and decreased respiratory drive might contribute to reduced genioglossal activation. Sleep deprivation itself depresses hypoxic and hypercapnic respiratory drives, which would tend to increase obstructive apneas if decreased respiratory drive also decreases genioglossal activation (74).

In summary, patients with OSA are predisposed to upper airway obstruction because they have small, high resistance oropharynxes. During sleep, activation of upper airway muscles falls, causing further reduction in cross-sectional area and even higher airflow resistance. High pharyngeal resistance causes negative pharyngeal pressure, drawing the tongue and oropharyngeal walls inward. Eventually, total occlusion and apnea result. Figure 17 summarizes the dynamic balance of forces affecting oropharyngeal patency.

Figure 17

FORCES ACTING TO OPEN AND CLOSE THE UPPER AIRWAY



Chest 86:114, 1984

DIAGNOSIS OF OSA

When evaluating patients for OSA, it is important to remember that apneas occur in many asymptomatic men over the age of 60 (75). To diagnose a sleep apnea syndrome, <u>both apneas and symptoms</u> must be present. Snoring and daytime sleepiness are the main reasons patients are evaluated for OSA. However, both symptoms are common in the general population, and both have low positive predictive value for a diagnosis of OSA (76,77). The current standard diagnostic test for OSA, polysomnography, is costly and time consuming. Thus, to avoid performing large numbers of unnecessary tests, it is helpful to screen potential OSA patients to identify those with high probability of having the syndrome. Some useful points for evaluating suspected OSA patients are listed on Table 8.

TABLE 8

APPROACH TO THE PATIENT WITH POSSIBLE OSA

1. Careful history, obtained from both the patient and the patients bedpartner.

2. Complete head and neck examination. Formal ENT evaluation may be indicated.

3. Awake arterial blood gas analysis and thyroid function tests.

As is usually the case, a good history is invaluable. The patient and the bedpartner should be asked about pre-sleep alcohol intake, nocturnal choking episodes, observed apneas, and severe somnolence. The latter is defined as uncontrollable sleepiness which interferes with the patients work and social life. Falling asleep while driving a motor vehicle is also an indication of severe somnolence. The presence of obesity, cor pulmonale, and arterial hypertension should be noted. Careful ENT examination, to detect a deviated septum, nasal polyps, hypertrophied tonsils, macroglossia, and micrognathia is especially important. These ENT abnormalities are surgically correctable causes of OSA. Hypothyroidism should always be excluded, since hypothyroid patients have the same signs and symptoms as OSA patients and also have obstructive apneas (78).

DIAGNOSTIC TESTS - Polysomnography, performed over a full nights sleep, is the gold standard test for OSA. Polysomnography can determine the type of apnea present, the apnea index, time spent in various sleep stages, and the number and severity of desaturations. Disadvantages of the test include its expense (about $1600 for a one night study) and limited availability of qualified sleep laboratories.

It is possible to screen for and diagnose OSA without doing polysomnography, and such an approach may be more cost-effective. A simple symptom score can be used to identify patients requiring further testing. A value of one is assigned for each of the following: observed apneas during sleep, nocturnal choking episodes, obesity, hypertension, and severe daytime somnolence. When 40 consecutive patients referred to a sleep center were evaluated by this simple score and polysomnography, all but two patients diagnosed as having OSA (apnea index >10/hr) by polysomnography had a score of 2 or more. The average symptom score of the OSA patients was four (79). Several investigators have used ear oximetry to detect OSA. An overnight ear oximetry study is cheap ($60), simple, and requires no elaborate equipment or specialized personnel. If one defines repetitive drops of >4% in oxygen saturation as abnormal, then oximetry is 66 to 80% sensitive and >90% specific (80-84). Furthermore, oximetry detects almost all patients with apnea indexes >20/hr, a group

with the greatest mortality and complication rates who would benefit the most from rapid diagnosis and treatment. Patients with COPD also have oxygen desaturation during sleep, and thus oximetry would not be a suitable screening test for a COPD patient suspected of having OSA. Combining results from these symptom score and oximetry studies, a reasonable strategy is to screen patients with a symptom score and, if the score is ≥ 2, perform overnight ear oximetry. Twenty to 34% of oximetric studies will be false negative, but most of these will occur in patients with mild OSA (i.e. apnea indexes <20/hr). Thus, if clinical suspicion is high, a negative oximetry study should be followed up with overnight polysomnography.

TREATMENT OF OSA

SELECTION OF APPROPRIATE TREATMENT - Patients with severe OSA (apnea index >20/hr) are at greatest risk, especially if they have already developed life threatening complications such as serious arrythmias or cor pulmonale. Such patients should be rapidly treated with one of two curative therapies - tracheostomy or continuous positive airway pressure (CPAP). The indications for treating patients with milder OSA are currently unclear. Treatment options for mild OSA include CPAP and a variety of other therapies. Weight loss should always be stressed for the obese OSA patient. Even modest weight loss of 8 to 10 kg has been shown to significantly reduce the apnea index (from 83 to 33/hr and from 55 to 29/hr in two different studies), but has little effect on symptoms (85). Weight loss also reduces pharyngeal compliance, which makes the oropharynx stiffer and more resistant to collapse. Dramatic weight loss, down to ideal body weight, is curative (86). Unfortunately, both initiating and maintaining even modest weight loss is often difficult for obese patients.

TRACHEOSTOMY - Tracheostomy was the first OSA treatment and is 100% effective because it bypasses the site of obstruction, allowing unimpeded airflow directly into the trachea (87). Experienced anesthesiologists and surgeons are important for successful surgery; routine pre-operative sedation should <u>never</u> be administered because sedation often precipitates respiratory arrest, and endotracheal tube placement is difficult (88). Dramatic improvements in daytime somnolence and other symptoms occur within days of surgery. Apneas and oxygen desaturations are abolished, and arrthymias and episodic rises in systemic and pulmonary artery pressure no longer occur (89,90). Patients can plug the tracheostomy during the day and need only open it before sleep.

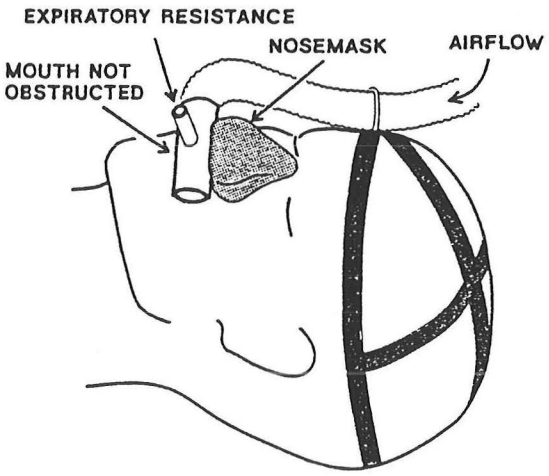
Post-operative complications include stoma site infection, psychological problems of adjusting to the tracheostomy, and granulation tissue formation at the stoma site. The latter causes hemoptysis and obstruction, often necessitating

tracheostomy revision. The incidence of complications seems to vary between centers, with some reporting only rare problems and others frequent problems. Up to 30% of patients have required tracheostomy revision in some reports (91). It is important that potential tracheostomy patients be able to perform routine daily stoma care , be mentally stable, and understand that the tracheostomy will likely be permanent; nocturnal tracheostomy closure results in recurrent OSA within days, and few patients have had successful tracheostomy closure. An interesting observation, supporting the concept that ventilatory drive in OSA is reduced secondary to sleep deprivation, is that tracheostomy restores the ventilatory response to carbon dioxide to normal in most OSA patients (92).

CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP) - CPAP therapy was first described in 1981 and has since become a widely used treatment modality (93). CPAP requires a custom fitted nasal mask connected to a blower capable of delivering a high volume flow (Figure 18). The pressure required to abolish apneas is determined empirically by increasing pressure until apneas cease; usually, only 4 to 16 cm H_2O pressure is required (94). CPAP effectively treats central, mixed, and obstructive apneas, snoring, and also corrects the chronic respiratory acidosis of OHS patients (95-98). CPAP basically works as a pneumatic upper airway splint by blowing the oropharynx open with positive pressure which prevents inspiratory collapse (99).

Figure 18

A CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP) DEVICE



In: Principles and Practice of Sleep Medicine, Chapter 59, p. 559, 1989

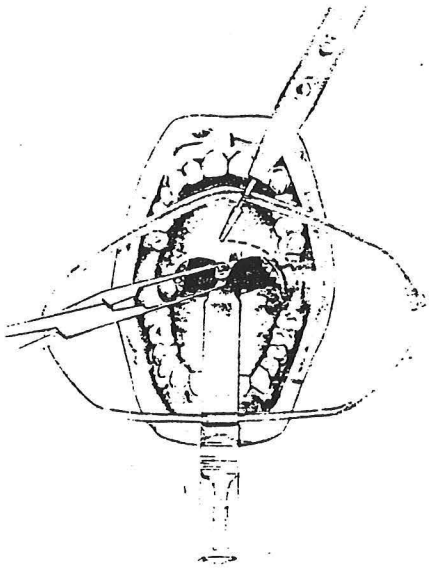
In common with tracheostomy, CPAP completely abolishes apneas, symptoms, and most OSA complications. It is important that only

tracheostomy and CPAP have been shown to reduce mortality (47). Unlike tracheostomy, CPAP has no serious side effects. Long term compliance with the cumbersome mask and tubing has been a problem. A common reason for discontinuing CPAP is discomfort, and physicians experienced with CPAP stress the importance of a comfortable, well fitting nasal mask for patient acceptance. One study followed 168 CPAP treated patients for 6 to 14 months and found that compliance varied with OSA severity. Patients with severe OSA felt so much better after starting CPAP that 90% continued to use it, whereas only 29% of those with mild symptoms continued (100). Every other night CPAP controls OSA well and may improve compliance (75).

UVULOPALATOPHARYNGOPLASTY (UPPP) - UPPP is a surgical therapy which removes the uvula , soft palate, and submucosal oropharyngeal soft tissue (Figure 19). UPPP cures snoring but is of limited efficacy for OSA. Data from three series of UPPP treated OSA patients show that only 42 to 45% had significant reductions in apnea index (101-103). Neither clinical features nor the presence of anatomic oropharyngeal abnormalities predict response to UPPP, and OSA actually worsens in some patients after surgery. Additionally, UPPP has not been shown to reduce mortality in severe OSA (47). Thus, it is difficult to recommend UPPP to most patients.

Figure 19

UVULOPALATOPHARYNGOPLASTY



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OXYGEN - Although not generally considered a therapy for OSA, administration of supplemental oxygen at night will prevent desaturations and arrthymias and will modestly reduce the number of apneas by 20 to 58% (104-106). Preventing desaturations with oxygen should also prevent pulmonary hypertension and cor pulmonale, although this has not been proven. Oxygen has little effect on daytime somnolence and should be given cautiously to OSA patients who also have OHS and retain carbon dioxide; these patients depend on hypoxic respiratory drive and may stop breathing when given oxygen. It is reasonable to administer oxygen to patients with mild OSA or to those who are unsuitable candidates for curative treatment with CPAP or tracheostomy.

OTHER THERAPY - Both progesterone and protriptyline have been used to treat OSA with mixed results. 60 to 120 mg/day progesterone resulted in significant reductions in the apnea index in 0 to 20% of patients; patients with daytime PaO_2 <60 mm Hg are most likely to improve (107-109). Protriptyline works by reducing the amount of REM sleep time, when apneas are longest. Protriptyline has little effect on the apnea index and its frequent anticholinergic side effects and arrythmogenic potential make it unsuitable for most OSA patients (110-112).

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