Sleep Apnea

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Obstructive sleep apnea is a common disorder characterized by repetitive collapse of the pharyngeal airway during sleep. The disorder results primarily from an anatomically small upper airway in conjunction with pharyngeal dilator muscles that can compensate for the anatomic deficiency awake, but not asleep. Ventilatory control instability and a low arousal threshold may contribute to the disorder as well. The consequences of sleep apnea fall into two domains: (*1*) neurocognitive dysfunction (sleepiness and decreased quality of life) resulting from sleep fragmentation and (*2*) cardiovascular disease (hypertension, stroke, myocardial infarction, and heart failure) likely resulting from the intermittent hypoxia. The disorder is generally diagnosed in the sleep laboratory over the course of a night, although alternative approaches in the home are also utilized. A number of treatment options are available. Continuous positive airway pressure remains the most consistently effective approach, although oral appliances (generally mandibular-advancing devices) and a number of surgical procedures have some demonstrated efficacy. Thus, therapy must be individualized to the patient's desires and the severity of the apnea.

Keywords: apnea; pharyngeal muscles; loop gain; diagnosis; treatment

This article provides an overview of the disorder obstructive sleep apnea (OSA). In so doing, four general topics will be addressed: (*1*) pathophysiology, (*2*) consequences, (*3*) diagnostic methodologies, and (*4*) treatment. However, first, it is worth noting that OSA is a common disorder that is present in at least 4% of adult men and 2% of adult women. Thus, there are a large number of patients suffering from this disorder.

As illustrated in Figure 1, OSA is characterized by recurrent collapse of the pharyngeal airway during sleep (1). As can be seen on the figure, respiratory effort is present and increasing over the course of the apnea, which is generally terminated by an arousal from sleep (2). Thus, these individuals wax and wane between apnea and hyperpnea and between sleep and wake. As can also be seen, the arterial oxygen saturation fluctuates up and down with the respiratory cycling.

PATHOPHYSIOLOGY

Obstructive apnea likely occurs in different patients for different reasons with four primary phenotypic traits likely explaining the presence or absence of OSA and its severity in most such patients. The traits are outlined in the following sections.

Anatomy

Most patients with OSA have an anatomically small pharyngeal airway (3–5). This may be due to obesity, bony structures, tonsils and adenoids, and so forth. However, anything that decreases pharyngeal airway size will increase the likelihood of developing sleep apnea. This reduced pharyngeal airway size has been demonstrated by a variety of techniques, including computed tomography, magnetic resonance imaging (Figure 2), and direct visualization of the airway awake and asleep with and without muscle activity present. All such studies indicate that patients with sleep apnea have an anatomically small airway, with obesity being the most common cause.

Pharyngeal Dilator Muscle Control Asleep

The upper airway is kept patent largely by the activity of a variety of pharyngeal dilator muscles, with the genioglossus muscle of the tongue being the best-studied such muscle (6, 7). These muscles respond to a variety of stimuli, including negative airway pressure and arterial chemistry (hypoxia and hypercapnia) (8–12). Negative airway pressure seems to be the primary stimulus to these muscles and allows the muscles to adapt to any threat to airway patency with active contraction, thereby dilating and protecting the airway. This has been convincingly demonstrated in iron lung (negative pressure) ventilators where respiratory input to the genioglossus muscle can be eliminated and the isolated relationship between airway negative pressure and muscle activation assessed (13). These studies indicate a close relationship between airway negative pressure and muscle activity. This mechanism is particularly active in the awake patient with sleep apnea whose anatomically small airway leads to increased negative airway pressure, thereby augmenting the activity of dilator muscles to maintain airway patency (14). Thus, patients with OSA have greater pharyngeal dilator muscle activity awake than do normal control subjects because their anatomy demands it. As a result, these patients breathe normally during wakefulness.

During sleep, this negative-pressure reflex that drives dilator muscle activity in the upper airway is substantially attenuated, although certainly not lost completely (15). With this sleep-induced decrease in reflex responsiveness, muscle activity falls in everyone at sleep onset. However, this leads to only small increments in airflow resistance in most normal subjects. In the patient with sleep apnea with reflex-driven elevations in muscle activity while awake, sleep induces a substantial decrement in dilator muscle activity, which leads to complete or near-complete pharyngeal collapse. Thus, the apnea or hypopnea begins. As a result, pharyngeal dilator muscles can compensate for the deficient airway anatomy of the patient with sleep apnea during wakefulness but not sleep.

Over the course of the apnea or hypopnea, progressively negative intrapharyngeal airway pressure develops as does rising P_{CO_2}. Both can drive upper airway muscle activity to some extent, even during sleep (16). Thus, one of several outcomes can occur. First, the optimal outcome would be that this augmenting muscle activity eventually opens the airway, allowing for adequate ventilation while sleep is maintained. If this occurs, relatively little disordered breathing will likely be encountered. Second, in many cases, adequate muscle activity cannot be recruited during sleep and arousal is required to reopen the airway (17). Thus, the individual cycles, as described above, between wake and sleep and between apnea and hyperpnea. Finally, the individual could asphyxiate due to the collapsed airway. Fortunately, this rarely, if ever, occurs.

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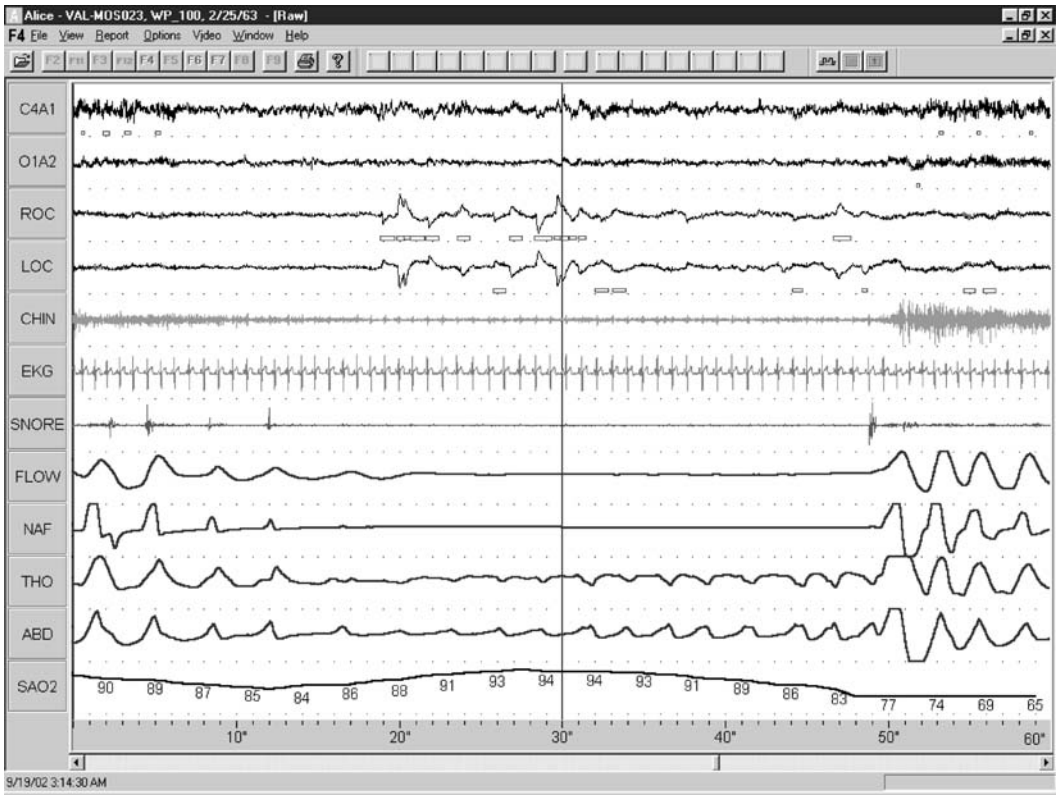

Figure 1. A 30-s episode of obstructive apnea occurring during REM sleep is demonstrated. Note the increasing ventilatory effort across the episode indicating its obstructive nature. Also note the sequelae of the episode: arousal from sleep and intermittent hypoxia.

The discussion above would suggest that individual variability in the ability of airway dilator muscles to be recruited during sleep and to open the airway without arousal may, in some cases, dictate who develops apnea and who does not. There are actually some early data supporting this concept in that individuals with identical anatomy but quite different muscle responsiveness asleep have been observed to have very different apnea severity. Thus, pharyngeal muscle control awake and asleep is quite important in apnea pathogenesis.

Arousal Threshold. On the basis of what has been said above, it should be clear that arousal is one important mechanism by which apneas can be terminated. On the other hand, if arousal is the only way to end an apnea, stable sleep will not likely occur in anyone with an anatomically small airway requiring neuromuscular compensation during wakefulness. That being said, it should be evident that a low arousal threshold (i.e., the individual awakens from sleep in response to minimal respiratory stimulation) could present a problem. Such an individual will not be able to stay asleep long enough to recruit upper airway muscle activity, thereby opening the airway (18).

Thus, phenotypic traits 2 and 3 interact. If an individual can recruit upper airway dilator muscles during sleep and can stay asleep long enough to do so, then airway patency can likely be achieved and maintained during stable sleep. If either of the

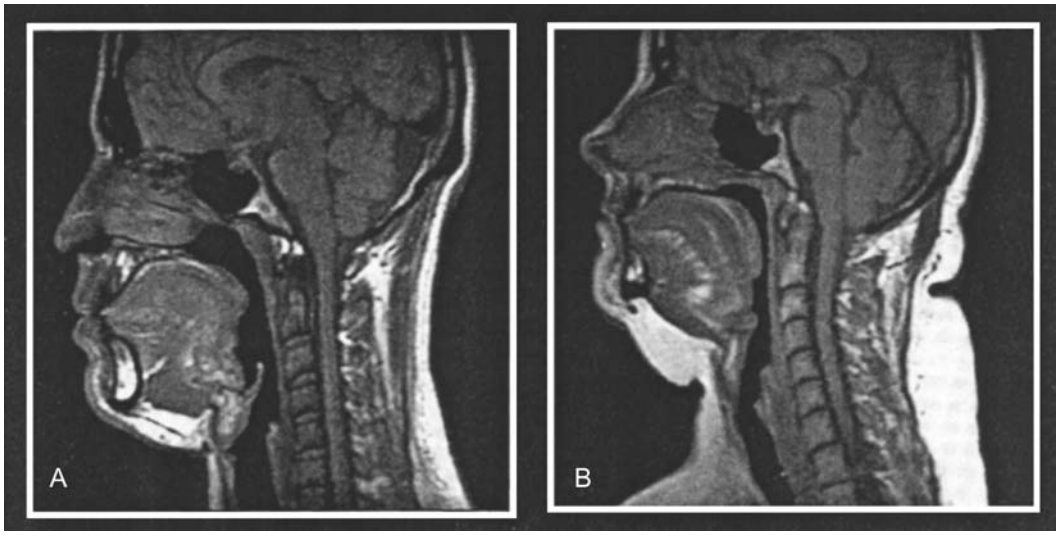

Figure 2. Sagittal magnetic resonance images from (*A*) a normal subject and (*B*) a patients with obstructive sleep apnea are demonstrated. Note that the airway behind the uvula, soft palate, and tongue are considerably smaller in the patient with apnea than the normal control subject. This is the site of pharyngeal collapse in the patient with apnea. Reprinted by permission from Schwab RJ. Upper airway imaging. *Clin Chest Med* 1998;19:33–54.

muscles cannot be recruited during sleep or the patient cannot stay asleep long enough to do so, then cycling apneas and hypopneas will likely develop. There are also clear data that the respiratory arousal threshold is quite variable between individuals, making this a potentially important phenotypic trait (19).

Loop Gain. There has been considerable argument over the years as to whether ventilatory control mechanisms play an important role in apnea pathogenesis (20, 21). The argument has been that upper airway dilator muscle activity is importantly influenced by respiratory drive. If respiratory drive is waxing and waning due to unstable ventilatory control, then airway patency may be compromised when respiratory drive is low. Thus, airway patency could wax and wane as well. Until recently, only the individual components of respiratory control stability could be measured, which provide limited information about overall ventilatory control stability. However, this has changed recently due primarily to the work of Madgy Younes and colleagues who clarified the concept of loop gain and its measurement to the respiratory community (21).

Loop gain is an engineering term used to quantify the gain of a system controlled by feedback loops. Respiration is certainly such a system, with this gain being influenced by controller variables (hypercapnic and hypoxic responsiveness), plant variables (ability to eliminate CO_2), and circulation time, among others. Simply put, loop gain can be defined as the response of a system divided by the disturbance leading to that response:

$$\text{Loop gain} = \frac{\text{response to a disturbance}}{\text{the disturbance itself}}$$

It should be evident from this formula that ventilation will become quite unstable when loop gain is more than 1. If the response is always greater than the disturbance, then ventilation can never stabilize and will wax and wane indefinitely. Thus, the higher the loop gain (the closer it is to 1), the potentially more unstable the respiratory control system will become.

There is an evolving literature that loop gain may be important in apnea pathogenesis in some individuals. Younes and colleagues have reported that patients with severe apnea have a higher loop gain than individuals with milder apnea. Hudgel and colleagues observed that patients with sleep apnea have higher loop gain than do normal control subjects (22). Finally, Wellman and coworkers recently reported that loop gain may importantly influence apnea severity only in patients with "moderate airway collapsibility" (Figure 3) (23). The concept is that patients with a highly collapsible airway will shut their airway at sleep onset regardless of loop gain. In patients with a minimally collapsible airway, respiratory-induced fluctuations in pharyngeal dilator muscle activity will not be enough to collapse the airway. It is only in the moderately collapsible group that loop gain becomes important. Thus, loop gain may be an important phenotypic trait in apnea pathogenesis in some patients.

Thus, various combinations of these four traits may yield OSA in different individuals. It should be stated, however, that a somewhat increased level of pharyngeal collapsibility is required for the development of OSA regardless of the other traits. If one's airway is patent when dilator muscle activity is absent, then the development of obstructive apnea is highly unlikely. However, once this threshold is crossed, the other traits likely become quite important.

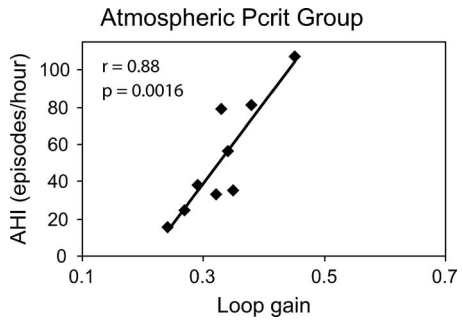

Figure 3. The relationship between apnea severity (apnea–hypopnea index [AHI]) and loop gain in patients with a moderately collapsible airway (Pcrit, −1 to +1 cm H_2O) is depicted. The relationship is strong in this group (r = 0.88). Reprinted by permission from Reference 23.

CONSEQUENCES

The consequences of OSA fall into two general categories: neurocognitive and cardiovascular. These will be addressed separately.

Neurocognitive. Sleep apnea clearly leads to increased sleepiness during the day and diminished cognitive function in the areas of attention/vigilance, learning and memory, and executive function (24). Whether the neurocognitive deficits are a product of sleep fragmentation and sleepiness or relate more to neural damage due to intermittent hypoxia is unclear at this time. It is also unclear how much of the neurocognitive dysfunction is reversible with therapy, although the sleepiness can certainly be improved with treatment of the apnea, with most such studies using continuous positive airway pressure (CPAP) to abolish the disordered breathing.

Cardiovascular. There is an evolving literature suggesting an association between OSA (primarily intermittent hypoxia) and a variety of adverse cardiovascular outcomes. These will be addressed individually.

Systemic hypertension. There is a substantial literature suggesting that OSA contributes to systemic hypertension with both epidemiology data and a useful animal model (25–28). Examples include prospective data from the Wisconsin Sleep Cohort reporting a dose–response relationship between apnea severity at one time point and the development of hypertension 4 to 5 yr later. This was the case after controlling for all known confounding variables. In addition, a dog model of sleep apnea developed diurnal hypertension after only 3 to 5 wk of simulated apnea. This resolved over several weeks after the apnea stopped. Finally, a number of studies have emerged indicating that treatment of sleep apnea leads to improvements in blood pressure (29–31). Thus, considerable data support a relationship between OSA and systemic hypertension.

Myocardial infarction, stroke, and congestive heart failure. The most comprehensive study to date to address the relationship between OSA and definitive endpoints relative to cardiovascular disease is the Sleep Heart Health Study. In this study, approximately 6,000 individuals, all current members of ongoing cardiovascular cohorts, had two full-night polysomnograms conducted 4 to 5 yr apart to assess the contribution of sleep apnea to adverse cardiovascular outcomes relative to other known risk factors. To date, only cross-sectional data are available, although longitudinal results should emerge in the years ahead (32). Using a parsimonious model, the group quartile with the most severe OSA (mean Respiratory Disturbance Index = $\sim$ 12–13 events/h) had an odds ratio of 1.27 ($p = 0.004$) for coronary heart disease, 2.38 ($p = 0.002$) for congestive heart failure, and 1.58 ($p = 0.03$) for stroke. Thus, these data strongly suggest that obstructive apnea contributes to the development of cardiovascular disease, although the longitudinal data are needed to be more definitive. Ultimately, randomized, double-blinded, placebo-controlled treatment trials are needed.

Despite the lack of definitive data firmly establishing a relationship between OSA and cardiovascular disease, a number of investigators have begun pursuing studies to assess the mechanisms by which sleep apnea or intermittent hypoxia might lead to atherosclerosis. These studies have reported elevated levels of adhesion molecules and adhesion indices in patients with OSA compared with control subjects. Markers of inflammation such as tumor necrosis factor α and C-reactive protein are also elevated in OSA (33, 34). Finally, there is clear evidence of increased lipid peroxidation or oxidative injury in sleep apnea, which returns to or near normal levels with CPAP treatment (35). Thus, there is increased reason to believe that sleep apnea contributes to the development of atherosclerosis with subsequent adverse cardiovascular outcomes.

DIAGNOSIS

There are a variety of ways in which OSA can be diagnosed. However, the criteria driving the clinical suspicion that sleep apnea may be present should be addressed first. These are outlined on Table 1, with loud snoring, witnessed apnea or gasping, and neck circumference being the strongest predictors of the disorder (36).

Once the suspicion of sleep apnea is adequate to further pursue the diagnosis, the most common and probably cost-effective approach is the in-laboratory split-night study. During the first 2 to 4 h of study, the patient is simply monitored for sleep-disordered breathing. If more than 20 apneas + hypopneas per hour are encountered, nasal CPAP is initiated and titrated to the level required to eliminate all disordered breathing, snoring, and flow limitation. This type of study can therefore be used to both diagnose OSA and determine appropriate CPAP pressure.

Other approaches, such as full-night diagnostic and full-night CPAP titrations, or a number of home diagnostic methodologies are currently used. The home diagnostic approaches vary from techniques as simple as oximetry to full polysomnography in the home. There are data to support each of these methodologies, although currently the major sleep societies do not advocate their routine use.

TREATMENT

Behavioral Approaches. A number of behavioral approaches are available to treat OSA. These include avoiding alcohol and sedatives near bedtime as these agents tend to aggravate apnea. Avoiding supine sleep may be all that is required in some patients, particularly those with mild apnea. Weight loss will improve or eliminate apnea in virtually all overweight patients as is evident after surgically induced weight loss. However, dietary weight loss is more difficult to accomplish and sustain and thus should not often be the only approach to patients with more than mild sleep apnea (37).

Nasal CPAP. The mainstay of therapy for OSA remains nasal CPAP, which works by pneumatically splinting the pharyngeal airway. CPAP is effective in virtually all patients and when consistently used can reverse or substantially reduce the subjective and objective sleepiness associated with OSA. Quality of life also generally improves, as does blood pressure if hypertension is present. Newer CPAP devices are able to "autotitrate," constantly determining the lowest pressure required to keep the airway open. Such devices may eliminate the need for CPAP titration in the laboratory. However, meta-analyses do not indicate that these devices treat apnea better than fixed-pressure devices nor do they consistently lead to better compliance (38). Thus, their role in apnea management is still somewhat unclear.

Oral Appliances. Most oral appliances used these days are designed to advance the mandible, thereby pulling the tongue structure forward and opening the pharyngeal airway. These devices are generally successful in reducing disordered breathing to an acceptable level about 40 to 60% of the time, with a greater percentage of patients having some improvement in Respiratory Disturbance Index. Although it was originally believed that oral appliances were only appropriate for patients with mild to moderate sleep apnea, not all current data support this stance, with some studies suggesting that patients with severe apnea may respond as frequently as those with mild apnea. Patients seem to prefer oral appliances to CPAP, although they are clearly not as consistently effective (39).

Upper Airway Surgery. Surgery of the upper airway generally represents a secondary approach to apnea therapy for patients who have failed other therapeutic methodologies. However, some patients prefer surgery and seek it as a primary approach.

Palatal surgery. Uvulopalatopharyngoplasty (UPPP) has been around for almost 25 yr, with most data suggesting a success rate (to an RDI < 20) of about 42% (40). Several lesser palatal surgeries subsequently emerged: first, laser-assisted uvuloplasty; and later, somnoplasty (a radio frequency [RF] procedure). The success rate with laser-assisted uvuloplasty was sufficiently low ($\sim$ 25–30%) that it is now rarely used to treat sleep apnea. RF treatment of the palate alone is also now uncommonly successful in treating OSA, although it does seem to improve snoring. However, snoring may recur over time. When RF of the palate and tongue base is combined, some patients are satisfactorily treated, although not enough data using this approach have been published to gain a real prospective on this procedure.

Mandibular surgery. Genioglossal advancement by resecting part of the mandible and placing it forward is generally combined with a UPPP and suspension of the hyoid, now most often down to the larynx. This combined procedure has a success rate approaching 60% in treating sleep apnea. The most aggressive procedure, bimaxillary advancement, involves breaking the mandible and advancing it about a centimeter. If this is done, the maxilla must be advanced as well or the teeth will not occlude. Thus, the whole lower face is moved forward. This procedure is also commonly combined with hyoid repositioning and may or may not include a UPPP before or during this procedure. Bimaxillary advancement is reported to have a success rate approaching 90%, although it is not available everywhere (41).

Thus, there are a number of therapeutic approaches available to treat sleep apnea and these should be individualized to the severity of apnea and the desire of the patient.

TABLE 1. CRITERIA SUGGESTING THE PRESENCE OF OBSTRUCTIVE SLEEP APNEA

Loud snoring
Witnessed apnea or gasping
Obesity (neck size $\geq$ 17 in in men and $\geq$ 16 in in women
Daytime sleepiness
Hypertension

Conflict of Interest Statement: D.P.W. is a consultant for Respironics, Inc. ($20,000/yr), Alfred E. Mann Foundation ($10,000/yr), Aspire Medical ($10,000/yr), Itamar Medical ($10,000/yr), PAVAD ($10,000/yr), and WideMed ($4,000/yr). He occasionally consults for Cephalon ($5,000) and Organon ($4,000). He has research grants from Respironics, Inc. (about $200,000/yr), Alfred E. Mann Foundation (about $30,000/yr), Cephalon (about $125,000/yr), and WideMed (about $10,000/yr).

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