Obstructive Sleep Apnea

David P. White[*1] *and Magdy K. Younes*[2]

ABSTRACT

Obstructive sleep apnea (OSA) is a common disorder characterized by repetitive collapse of the pharyngeal airway during sleep. Control of pharyngeal patency is a complex process relating primarily to basic anatomy and the activity of many pharyngeal dilator muscles. The control of these muscles is regulated by a number of processes including respiratory drive, negative pressure reflexes, and state (sleep) effects. In general, patients with OSA have an anatomically small airway the patency of which is maintained during wakefulness by reflex-driven augmented dilator muscle activation. At sleep onset, muscle activity falls, thereby compromising the upper airway. However, recent data suggest that the mechanism of OSA differs substantially among patients, with variable contributions from several physiologic characteristics including, among others: level of upper airway dilator muscle activation required to open the airway, increase in chemical drive required to recruit the pharyngeal muscles, chemical control loop gain, and arousal threshold. Thus, the cause of sleep apnea likely varies substantially between patients. Other physiologic mechanisms likely contributing to OSA pathogenesis include falling lung volume during sleep, shifts in blood volume from peripheral tissues to the neck, and airway edema. Apnea severity may progress over time, likely due to weight gain, muscle/nerve injury, aging effects on airway anatomy/collapsibility, and changes in ventilatory control stability.
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Description of the Clinical Disorder

Obstructive sleep apnea (OSA) is a common disorder characterized by repetitive collapse of the pharyngeal airway during sleep (Fig. 1). Afflicted individuals generally breathe quite normally during wakefulness, but cannot maintain airway patency during sleep. The site of collapse is most often behind the uvula, soft palate, or tongue or some combination of these structures. Arousal from sleep is usually observed at the time of airway opening, although this is not always the case. In association with these pauses in respiration, hypoxia and hypercapnia generally develop and can be severe. Thus, the individual cycles during the night between apnea and hyperpnea, with the associated intermittent hypoxia and hypercapnia, and between sleep and wakefulness (142).

Individuals with sleep apnea often present with complaints of loud snoring, witnessed gasping, choking, or apnea, and daytime sleepiness. They may also have morning headaches, sexual dysfunction, and depression. Patients with such complaints are then referred to a sleep laboratory where an overnight study is conducted during which sleep, respiration plus respiratory effort, oxygen saturation, EKG, and leg electromyogram (EMG) are monitored. During this study, abnormal respiratory events are quantified as apneas and hypopneas. An apnea is a 10 s or longer complete cessation of breathing while an hypopnea is similar, but respiration does not stop completely. Generally, a hypopnea is only scored if there is an associated decrement in arterial oxygen saturation of 3% to 4% or an arousal from sleep (97). The number of apneas plus hypopneas per hour of sleep is called the apnea-hypopnea index (AHI). By convention, an AHI greater than 5 is considered abnormal. The combination of an AHI greater than 5 plus daytime symptoms is required for a diagnosis of OSA syndrome. An AHI of 5 to 15 is considered mild, 15 to 30 moderate, and greater than 30 severe OSA.

Epidemiology

The most comprehensive data to date suggest that OSA (AHI $>$ 15) occurs in approximately 2% to 14% of the adult population, depending on gender and ethnicity (304, 305). Prevalence may be higher in African Americans (196). If symptoms are not required, 24% of men and 9% of women have an AHI greater than 5. However, this study was published in 1993, and the rates of obesity, one of the major drivers of OSA (see later), have increased substantially. More current estimates are that 20% of adults have mild OSA (AHI 5-15) and 6% to 7% have moderate to severe OSA (AHI $>$ 15) (305). Thus, it is a common disorder.

The occurrence of sleep apnea has been associated with a number of traits with body mass index (BMI) or, more specifically central obesity, demonstrating the strongest such association (168). In both men and women, there is a direct

[*]Correspondence to dpwhite@partners.org

[1]Harvard Medical School and Brigham and Women's Hospital, Boston, Massachusetts

[2]University of Manitoba and Research Professor, University of Calgary, Calgary, Alberta, Canada

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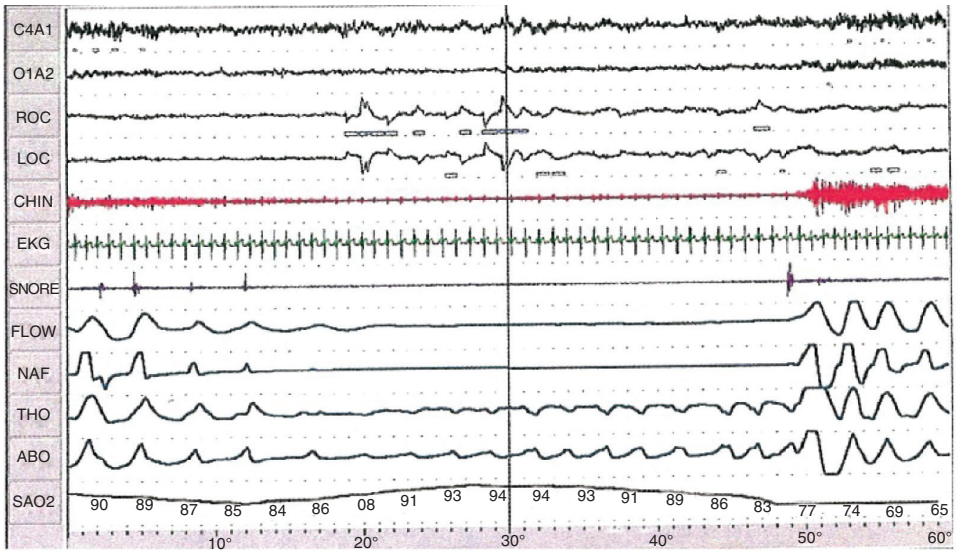

Figure 1 Shown is a one minute recording of rapid eye movement (REM) sleep demonstrating an approximately 30 s obstructive apnea with arterial oxygen desaturation and arousal at the termination. The channels recorded are: electroencephalography (EEG) (C4A1 and 01A2), eye movement [right occulogram (ROC) and left occulogram (LOC)], Chin EMG, electrocardiography (EKG), sound (snore), thermister flow (FLOW), nasal pressure (NAF), thoracic and abdominal motion (THO and ABD), and oxygen saturation (SAO_2).

correlation between BMI and apnea presence and severity. It has been estimated that in 41% to 58% of adults suffering from OSA, having the disorder is directly attributable to obesity (142, 168). Weight loss also consistently leads to a reduction in AHI (Fig. 2). There is also a substantial gender effect, with males having OSA 2 to 3 times more often than women. However, the prevalence of sleep apnea in women increases after menopause and has been attributed by some to reduced estrogen (228). The prevalence of sleep apnea also increases substantially with aging, from age 35 to about 60, when this increment begins to level off (Fig. 3) (306). Although ethnicity has been reported to contribute to apnea prevalence, most data suggest that this effect is mediated through body habitus and not ethnicity *per se*.

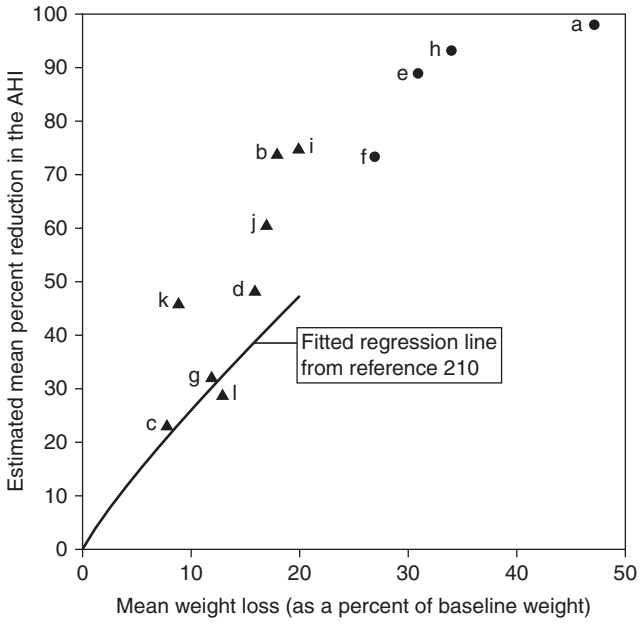

Figure 2 Estimated mean apnea-hypopnea index (AHI) reduction (as a percentage of baseline AHI) associated with mean weight loss (as a percentage of baseline weight) from clinical studies of dietary weight loss (*triangles*), surgical weight loss (*circles*), and one population-based observational study of weight change (*fitted regression line*). Note that the *regression line* is fitted to individual observations from Peppard and co-workers and is not fitted to the points (representing other studies) in the figure. Adapted, with permission, from reference 305.

Clinical Consequences

The clinical consequences of OSA fall into two general categories, neurocognitive and the cardiovascular. The neurocognitive problems are believed to result from the sleep

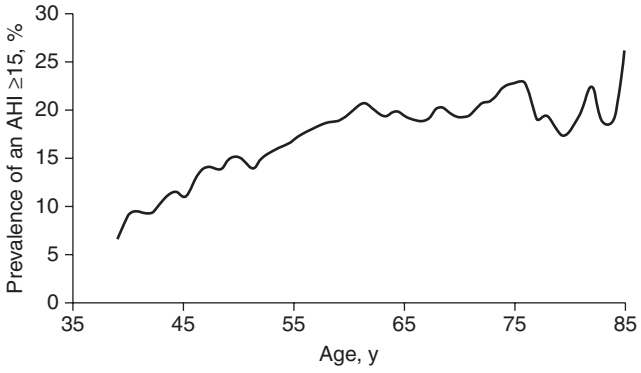

Figure 3 Smoothed plot (5-year moving average) of the prevalence of an apnea-hypopnea index (AHI) of 15 or greater by age. Adapted, with permission, from reference 305.

disruption resulting from sleep apnea, while most evidence would suggest that the adverse cardiovascular outcomes are a product of the intermittent hypoxia. However, neither conclusion has been fully demonstrated. Adverse neurocognitive outcomes include daytime sleepiness, reduced attention, increased automobile and industrial accidents, and generally decreased quality of life (56). Most of these problems can be substantially reduced with therapy of the apnea, although not necessarily normalized (8).

The potential cardiovascular consequences of OSA include hypertension (187), diabetes (195), cardiac arrhythmias, strokes (197), myocardial infarction (143), and the development of congestive heart failure (79). The data supporting the association between sleep apnea and these adverse outcomes include cross sectional and longitudinal studies, in addition to therapeutic case series. However, there have been no randomized, controlled trials assessing the effect of therapy of OSA on hard endpoint cardiovascular outcomes. As a result, the association between OSA and heart/vascular disease cannot be considered definitive at this time.

Treatment

The current principal therapy for OSA is continuous positive airway pressure (CPAP) that is most commonly delivered through a nasal mask, although nasal pillows and masks covering both the nose and mouth are frequently used as well (245). CPAP is believed to simply pneumatically split open the pharyngeal airway, thereby allowing for rhythmic breathing during sleep. CPAP is virtually 100% effective in apnea therapy, with its primary limitation being compliance. Many patients simply are unable to use CPAP on a sufficiently regular basis to make it an effective therapy for them (120). When CPAP cannot be tolerated, other approaches must be considered, which generally consist of oral appliances (46) and upper airway surgery (111, 233). The most commonly used oral appliance is a mandibular advancing device most often fabricated by a dentist. Advancing the mandible will pull the tongue forward, thereby enlarging the retroglossal airspace. These devices are reasonably effective in treating OSA, particularly for patients with mild to moderately severe disease.

There are now a variety of surgical procedures designed to treat OSA by enlarging the retrolingual or retroglossal airspace, generally by either removing tissue or changing its position. Most such procedures are aimed at either removing or reducing the size of the soft palate or advancing the position of the tongue. Although a number of these procedures are reasonably effective at treating snoring, short of aggressive surgery (or tracheostomy), OSA is rarely cured by these surgeries. As a result, surgery remains a secondary approach to apnea therapy.

A variety of additional approaches to apnea therapy have evolved over the years and include weight loss (by diet or surgery) (168, 305), control of sleeping position (75) (to avoid supine sleep), maximizing nasal patency, and avoiding alcohol (251) and sedatives near bed time. However, none of these therapies (short of substantial weight loss) is particularly effective at eliminating OSA. As a result, these approaches are most often used in conjunction with the other treatments described earlier.

Pathophysiology of Obstructive Sleep Apnea

The human upper airway

Normal anatomy

The human upper airway is a complex structure extending from the external nares to the epiglottis. The main site of collapse in patients with OSA ranges from the back of the nasal septum or choannae to the epiglottis, with most such collapse occurring behind either the uvula/soft palate or behind the tongue (36, 108). Commonly both are involved. Collapse at the level of the epiglottis may also occur (110).

Although a detailed description of upper airway anatomy is provided elsewhere (Malhotra Chapter in C.P.), the topic will be briefly addressed here. The principal components of the upper airway are the nose, the nasopharynx, the retropalatal oropharynx, the retroglossal oropharynx, the hypopharynx, and the larynx (Fig. 4). The larynx will not be addressed in this review.

In normal individuals, the *nose* is the site of the greatest resistance in the entire airway, with most of that resistance occurring in what is called the nasal valve. As shown in Figure 5, the lateral walls of the nose are made up of the inferior, middle, and superior turbinates/chonchae, while the medial wall is the nasal septum. Although, as stated above, the nose may add considerable resistance to inspiratory airflow, the nose itself is not a site of collapse in patients with OSA. This is likely because nasal patency is generally maintained by the cartilaginous structure surrounding the nose, and is therefore minimally dependent on muscle activity. Thus, nasal resistance is not significantly affected by sleep. As a result, the nose will not be addressed in detail here. However, as will be discussed later, increasing nasal resistance can lead to more negative intrapharyngeal pressure that may contribute to pharyngeal collapse in other sites. The *nasopharynx* runs from the end of the nasal turbinates to the hard palate and also does not generally contribute to pharyngeal collapse.

The *oropharynx* runs from the hard palate to the epiglottis and is often divided into the retropalatal and retroglossal components that are separated by the caudal end of the soft palate. The anterior wall of the oropharynx is made up of the soft palate and the tongue, while the posterior wall is composed of the superior, middle, and inferior constrictor muscles. The lateral pharyngeal walls are composed primarily of muscular tissue (constrictors, palatoglossus, palatopharyngeus, styloglossus, stylohyoid, stylopharyngeus, and hyoglossus). Lymphoid tissue may be present as well. Although most evidence would suggest that the oropharynx will remain patent

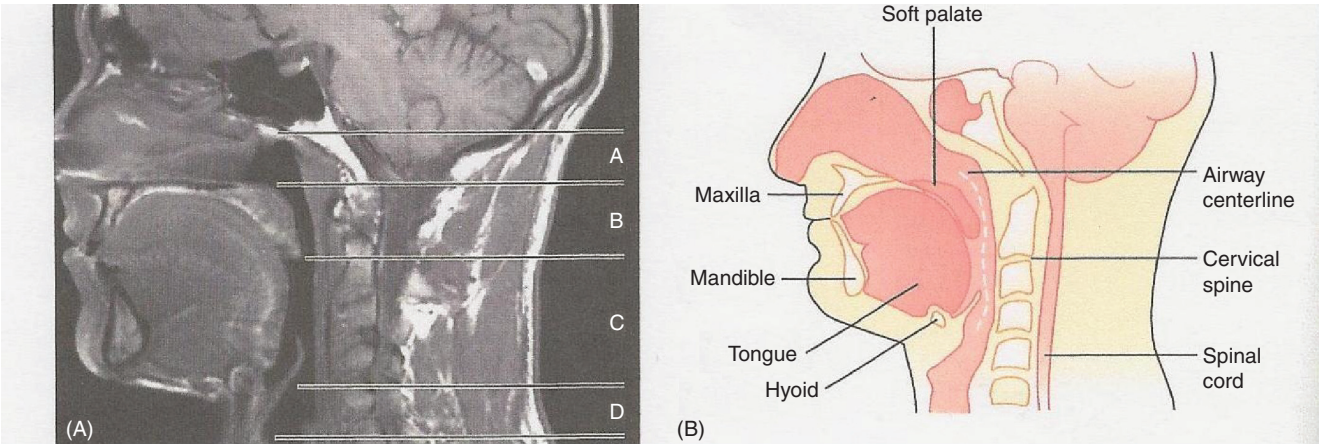

Figure 4 (A) Midsagittal MRI in a normal subject, highlighting the four upper airway regions: the nasopharynx, which is defined from the nasal turbinates to the hard palate; the retropalatal (RP) oropharynx, extending from the hard palate to the caudal margin of the soft palate; the retroglossal (RG) region from the caudal margin of the soft palate to the base of the epiglottis; and the hypopharynx, which is defined from the base of the tongue to the larynx. (B) The diagram demonstrates important midsagital upper airway, soft tissue, and bone structures. Adapted, with permission, from reference 214.

in most normal individuals in the absence of muscle activity (101), the muscles which surround this portion of the airway can significantly influence its shape and size. As the oropharynx is the primary site for airway collapse in patients with OSA, control of the muscles that make up the airway walls is important in sleep apnea pathogenesis. This portion of the airway will be the focus of much of the discussion in this review.

The *hypopharynx* runs from the base of the epiglottis to the larynx and esophageal opening. It, like the nasopharynx, is not commonly part of the collapsing segment in patients with OSA and will thus not be addressed further here.

Normal role and control of the pharyngeal musculature

A substantial number of muscles are involved in controlling the pharyngeal airway and facilitating the multiple functions in which this portion of the airway participates. The primary such functions are breathing, speech, and swallowing. As this review addresses the disorder OSA, the focus will be on the respiratory function of these muscles and their ability to keep the airway open, allowing air movement and thereby gas exchange in the lung. There are four major groups of muscles that are involved, more or less, in this respiratory function. These include:

1. Muscles controlling tongue position and shape.
2. Muscles controlling palatal shape and position.
3. Muscles influencing hyoid bone position.
4. Pharyngeal constrictor muscles.

Although each muscle will be addressed, there is substantial variability in the information available, with some muscles being well studied and others minimally so. For each muscle, the following information, if available, will be provided:

- Basic activation pattern of the muscle. Is there greater activity during inspiration than expiration (inspiratory or expiratory phasic pattern) or no respiratory modulation (tonic pattern)?
- Local reflex control mechanisms influencing muscle activity.
- Response of the muscle to respiratory stimulation.
- Influence of sleep [nonrapid eye movement (NREM) and REM)] on muscle activation and responsiveness to local and respiratory stimuli.

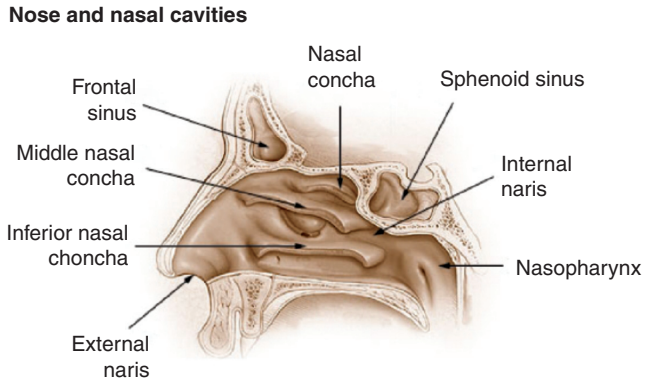

Figure 5 The nose and nasal cavities are illustrated. The nasal value, the highest resistance portion of the upper airway, lies just inside the external nares shown in the figure.

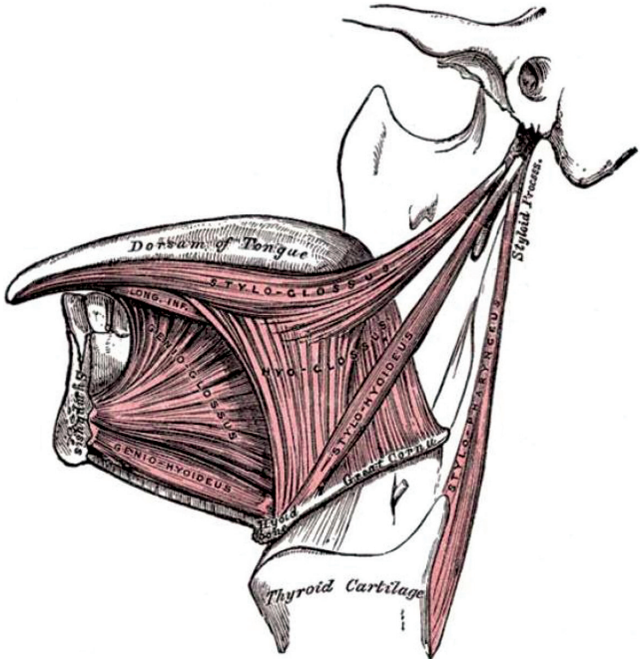

Figure 6 Illustrated are the extrensic muscles of the tongue. The primary protruders are the genioglossus and geniohyoid, while the primary retractors are the myoglossus and styloglossus.

Muscles controlling tongue position and shape (Fig. 6)

Although there are numerous intrinsic muscles in the tongue itself, most of these dictate tongue protrusion and shape and may not be directly involved in the respiratory function of the tongue or in maintaining airway patency. However, data from anesthetized rats indicate that intrinsic tongue muscles can demonstrate respiratory modulation when the animal is studied under hypercapnic conditions (11) and when mildly hypoxic (13). In addition, data from this same laboratory, again in rats, suggest that activation of the intrinsic tongue muscles increases velopharyngeal airway volume (12). Thus, a role for these intrinsic muscles in the control of airway patency cannot be excluded. As a result, studies in humans to assess this possibility are needed.

Genioglossus

The genioglossus (GG), a protruder muscle of the tongue, is by far the best studied upper airway muscle, at least as relates to respiration and sleep apnea pathogenesis. Its origin is the geniod turburcle of the mandible and it inserts into the base of the tongue. It is innervated by the hypoglossal (12th cranial) nerve. Virtually all studies to date indicate that this muscle, during EMG recordings, has an inspiratory phasic pattern of activation, with tonic activity present during expiration (210,252). This activation pattern has been observed for years using multiunit recording techniques. However, it must be recognized that there are important limitations to multiunit EMG recordings. These include, among others, correct (reproducible) positioning of the electrodes, averaging of the signal over time, and comparisons of muscle activity between subjects for which there is no standardized technique. More recent single motor unit (SMU) recordings indicate a quite complex muscle behavior (209), with six different firing patterns being observed (inspiratory phasic, inspiratory tonic, expiratory phasic, expiratory tonic, tonic, and tonic other).

There are at least three sources of stimuli that can activate the GG muscle. These will be discussed in a physiologic manner here, with their neurobiologic source being addressed in another review (Horner Review in Compre. Physiol.). These include local reflexes sensitive to negative pressure, respiratory drive (baseline and in response to rising PCO_2 or falling Po_2), and state (wakefulness versus sleep). Each will be addressed separately.

For years, animal data using an isolated upper airway demonstrated that the application of negative pressure to the upper airway could activate the GG muscle (148, 149). This was ultimately demonstrated in man using rapid onset pulses of negative pressure that led to rapid activation of this muscle (91, 277). Subsequent studies in humans, using a negative pressure ventilator to eliminate respiratory drive, demonstrated close synchronization across inspiration of negative pressure in the airway and the activity level of the GG (Fig. 7) (4).

Several lines of evidence suggest that the hypoglossal nucleus also receives direct neural input from the respiratory pattern generating neurons in the brainstem. First, the GG, on virtually all breaths, activates prior (50-100 ms) to the diaphragm or the start of inspiratory flow (266). As pressure in the airway is always either zero or positive at this time, the negative pressure reflex cannot be responsible for this muscle activity. Therefore, it must come from a respiratory oscillator. Second, both hypoxia and hypercapnia lead to increased GG activity (184,266). Although it could be argued that more negative airway pressure resulting from increased pump muscle activity could be responsible for this observation, augmented GG EMG has also been observed with hypercapnia, when airway pressure was kept positive using a continuous CPAP device (134). Finally, when patients with a tracheostomy are studied (138), there is still inspiratory phasic activation of the GG even when all airflow (and pressure) is diverted away from the upper airway (and out the tracheostomy). Thus, considerable evidence supports the notion of direct respiratory modulation of the GG muscle.

The evidence that state (wakefulness versus sleep) directly influences the GG muscle has been difficult to prove, as there are many variables changing simultaneously when an individual falls asleep. That GG EMG is reduced with sleep onset in normal subjects is quite clear (157, 289). What is driving this decrement in muscle activity is less clear. There could be decreased intrapharyngeal negative pressure due to reduced respiratory drive at sleep onset that might yield diminished reflex input to the muscle. The loss of respiratory drive itself could also decrease GG activation. The most convincing evidence of a pure state effect was the decrement in genioglossal

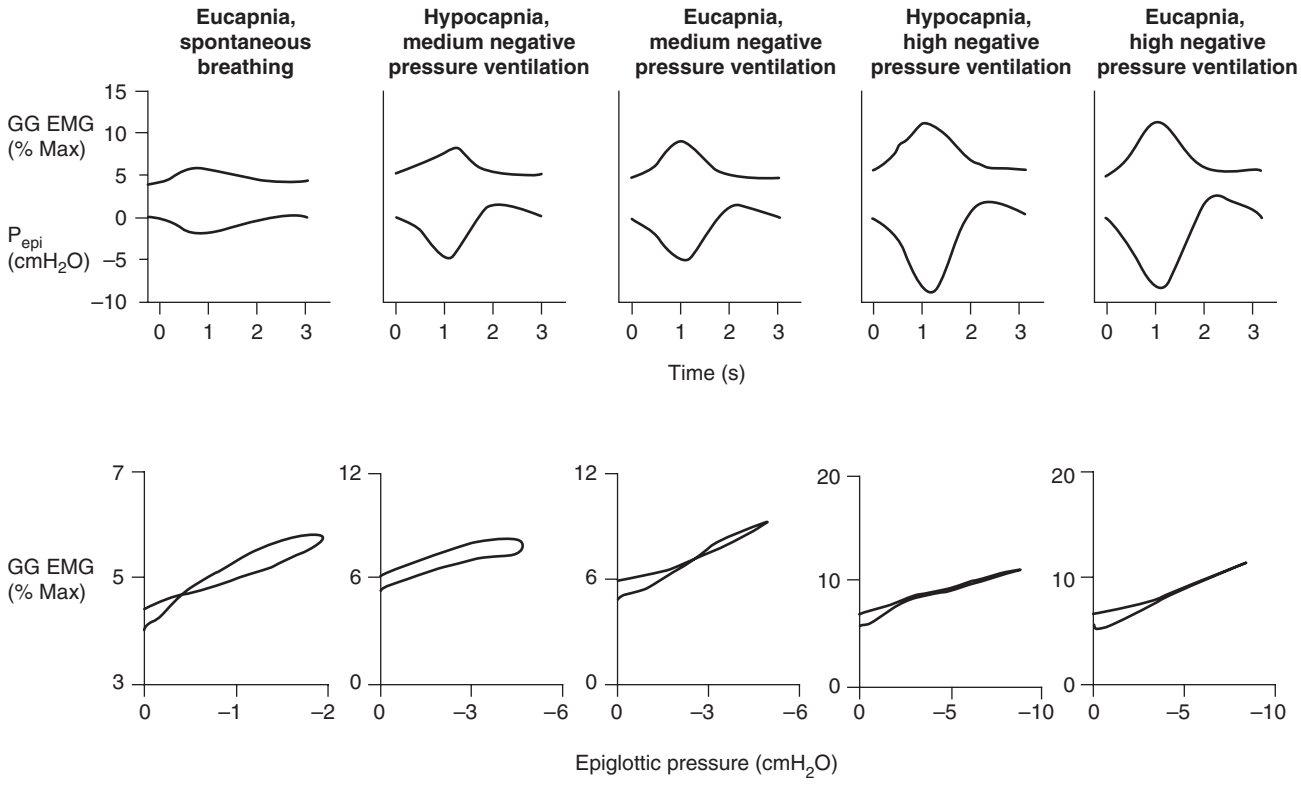

Figure 7 The group mean relationships between negative pressure at the epiglottis (P_{epi}) and genioglossal electromyogram (EMG) (GG EMG) are shown. In each condition there is a highly significant relationship between P_{epi} and GG EMG throughout inspiration. This can be seen both in the plot of both signals against time (upper panels) and in the *x-y* plots (lower panels). The mean slopes of the relationships between negative P_{epi} and GG EMG were very similar among conditions within each experiment. Nonetheless, there was invariably some degree of "hysteresis", whereby GG EMG changed relatively more for a given change in P_{epi} early in inspiration. Adapted, with permission, from reference 4.

activity observed in normal individuals who fell asleep while being mechanically ventilated noninvasively, (NIV, thus there was no respiratory drive) with adequate continuous positive pressure in the airway to eliminate negative pressure muscle activation (133). The results of this study suggest that wakefulness itself, apart from respiratory and reflex mechanisms, augments genioglossal activity.

As stated earlier, the best evidence available suggests that there is a decrement in GG EMG at the sleep onset (early NREM sleep) in normal subjects. Over time asleep, muscle activity commonly increases and is often found to be higher during stable NREM sleep than is encountered during wakefulness (16). However, this likely reflects a muscle response to the increased negative pressure in the airway and higher arterial PCO_2 encountered during sleep, rather than an effect of sleep itself. The effect of REM sleep on GG EMG is a bit more controversial. Early studies suggested that GG activity during tonic REM sleep (no eye movements) is quite similar to that observed during NREM sleep and that muscle activity only fell from this NREM level in close association with REMs (283). Other evidence indicates that GG activation is generally reduced in REM as compared to NREM sleep (60). The difference in these studies may reflect the use of CPAP and/or NIV in some studies and not others.

Based on brainstem recordings in cats, it was proposed that the decrement in GG EMG was likely the product of a decreased firing frequency in respiratory neurons with a tonic (not inspiratory) firing pattern (178). Respiratory neurons with strong inspiratory firing generally maintained their firing frequency better during NREM sleep. However, this concept could not be tested in humans using multiunit EMG recordings. Recent SMU recording in normal subjects does not support this hypothesis. In these studies, tonic units actually increase their mean firing frequency in the transition from wakefulness to NREM sleep and only rarely cease firing altogether (Fig. 8) (285). On the other hand, units that fire more rapidly or only during inspiration (inspiratory tonic and inspiratory phasic units) commonly quit firing completely either in the wake-sleep transition or during more stable NREM sleep (285). Thus, NREM sleep affects the various motoneurons innervating the GG quite differently depending on firing patterns. To date there have been no SMU recordings from the GG during REM sleep.

There is a reasonably substantial literature addressing the ability of the GG muscle to respond to various stimuli during sleep as opposed to wakefulness. Early studies applying pulses of negative pressure to the pharyngeal airway in man suggested a robust response when awake, but a marked

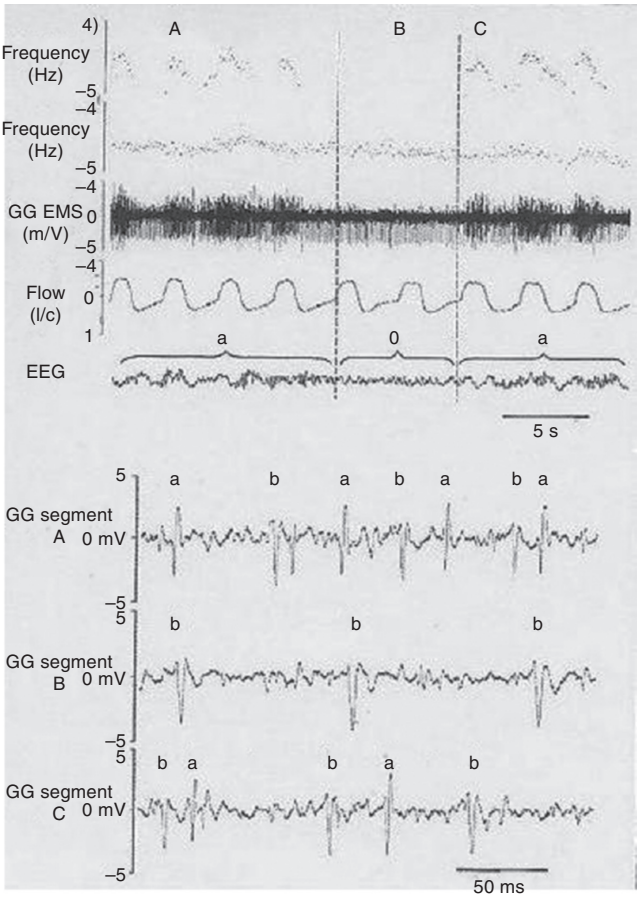

Figure 8 The top panel shows the instantaneous frequency plots for 2 motor units recorded on the same electrode before and after alpha to theta and theta to alpha transitions. Also shown are the raw electromyogram (EMG), airflow, and the electroencephalogram (EEG) recordings. Vertical lines indicate state transitions. The figure illustrates the differential effects of the alpha to theta transition on inspiratory phasic (top tracing) and tonic (second tracing) motor units and shows that the cessation of the inspiratory phasic unit was not a consequence of electrode movement. The bottom panel shows typical individual spikes for the 2 motor units illustrated in the top panel at points A, B, and C (a is the inspiratory phasic unit and b, the tonic unit). Adapted, with permission, from reference 285.

decrement in the ability of the muscle to respond to negative pressure during stable NREM sleep (90, 277). Similar studies during REM sleep indicated a further decrement in this reflex muscle responsiveness or even inhibition of muscle activity when negative pressure was applied (229). Protocols conducted in an iron lung (negative pressure ventilator to eliminate respiratory input to the muscle), as described earlier, support this concept, as the slope of the relationship between GG EMG versus airway negative pressure is considerably flatter (lower slope) during NREM sleep than wakefulness (70). However, Loewen et al. (136) observed a brink genioglossal response to negative pressure during NREM sleep once a threshold level of chemical drive had been achieved. Thus, it is probably safe to conclude that this muscle is considerably less responsive to negative pressure during sleep, particularly REM sleep, than it is during wakefulness, but can be quite responsive once a certain level of ventilatory drive has been achieved.

It has been known for some time that both hypoxia (176) and hypercapnia (175) can markedly increase the activity of the GG muscle during wakefulness. However, there are fewer studies in man assessing the ability of the GG to respond to these chemical stimuli during sleep. The first study to make this determination reported no statistically significant response to either elevated PCO_2 or reduced PO_2 in isolation during NREM sleep (241). However, the combination of hypercapnia plus inspiratory resistive loading led to a significant increase in muscle activity. What was actually driving the increased GG EMG in the last experiment, airway negative pressure or elevated PCO_2, was never resolved. A more recent study conducted on nasal CPAP, to eliminate any influence from airway negative pressure, reported an increase in muscle activity with an elevation in PCO_2 (134). On the other hand, Loewen et al. (136) observed minimal response of the GG muscle to increased chemical drive during NREM sleep in subjects on adequate CPAP to prevent negative pressure generation in the airway. Thus, it seems most likely that the muscle responsiveness to chemical stimuli during NREM sleep is substantially reduced, as was the case with negative pressure. There have been no studies assessing chemical responsiveness of this muscle during REM sleep.

Despite the observations described above, it seems clear that the GG muscle can substantially increase its activity when challenged during NREM sleep. If an inspiratory resistive load is applied externally during stable NREM sleep and GG EMG is followed over time, there is a marked increase in muscle activation, although this often requires a number of breaths (30-60 s) to occur (282). If airway pressure is dropped, again during stable NREM sleep, from a holding pressure (that required to maintain airway patency without flow limitation), to a less positive or an actually negative airway pressure (usually associated with flow limitation) the muscle can respond relatively quickly, generally within 2 to 3 breaths, and robustly (106). As this is the challenge that the muscle will face under natural sleeping conditions (increased airflow resistance/partial airway collapse with elevated chemical drive), it would seem that the muscle can respond to such a challenge in an attempt to maintain airway patency. This is consistent with the work of Loewen et al. (136), suggesting that the muscle can respond rapidly once a threshold level of chemical drive has been achieved. However, there is considerable variability in this response from one normal subject to the next, with some responding briskly and others not at all.

Hyoglossus

The hyoglossus muscle runs from the hyoid bone to the base of the tongue and is innervated by the hypoglossal nerve. It is believed to both retract and lower (depress) the tongue. There are few studies in man of this muscle, but those available do not indicate that this muscle has respiratory modulation during resting ventilation (147). However, data from rats suggest

that inspiratory activation can be seen under basal conditions and increases with exposure to hypoxia or hypercapnia (11, 13). In humans, breath holding led to a substantial rise in the activation of this muscle. In addition, a combination of hypoxia and hypercapnia produced increased muscle activity, with an inspiratory phasic pattern (147). Thus, this muscle can clearly respond to respiratory stimulation in all species examined.

A number of studies have assessed the effects of stimulating a retractor muscle (the hyoglossus), a protruder muscle (the GG), or a combination of both on pharyngeal mechanics. Data from rats suggest that isolated retractor stimulation has little effect on these mechanics, while protruder stimulation improved flow but not collapsibility (74). However, when both are stimulated flow increases and the airway becomes less collapsible (74), an effect that is larger than was seen with protruder stimulation alone. Human data (171) indicate that protruder stimulation yields reduced airway collapsibility while retractor stimulation increases collapsibility. When both are stimulated, the effect is similar to that seen with protruder stimulation alone. Thus, one would conclude that the protruder and retractor muscles are commonly activated simultaneously, particularly in response to respiratory stimuli, and that this combined activation stiffens the airway, yielding reduced collapsibility.

Styloglossus

The styloglossus muscle runs from the styloid process of the temporal bone to the tongue (Fig. 6) and is innervated by the hypoglossal nerve. When activated, it will both retract and elevate the base of the tongue. There are few studies assessing the respiratory role of this muscle is either humans or animals. However, one study in anesthetized dogs demonstrated inspiratory phasic activation of the styloglossus muscle during both hypoxia and hypercapnia (291). Thus, it is probably not unreasonable to assume that it is activated similarly to the hyoglossus, although firm data to document this do not exist.

Muscles controlling palatal shape and position (Fig. 9)

The shape and position of the palate are controlled primarily by five muscles. The palatal arch muscles, the *palatoglossus* and *palatopharyngeus*, pull the palate down onto the base of the tongue, thereby both opening the retropalatal airway and facilitating nasal ventilation. Obviously, oral ventilation is inhibited. The *levator palatini* muscle elevates the palate and thus moves it into the retropalatal airway, thereby inhibiting nasal ventilation and facilitating oral respiration. The function of the *tensor palatini* (TP) is argued, with some data suggesting that it contributes to moving the palate off the posterior pharyngeal wall, thereby reducing airflow resistance through the upper airway. Others believe, based primarily on the origin and insertion of the muscle, that it does little more than stiffen the palate. Finally, the *musculus uvulae* lies in the body of the soft palate and uvula and is believed to influence the shape of the palate primarily in its role of optimally closing off the nasal from the oral airway during oral respiration, speech, and swallowing.

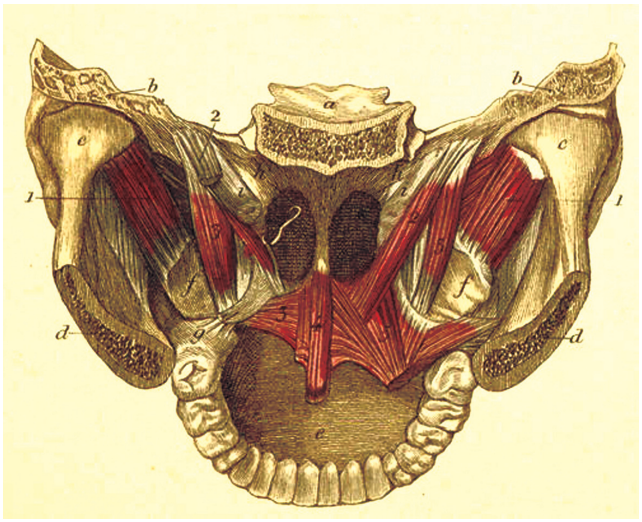

Figure 9 Demonstrated are the muscles of the soft palate: (2) levator palatini; (3) tensor palatini; (4) musculus uvula; and (5) palatopharyngeus. The palatoglossus is not shown. Also shown is: (1) external pterygoid. Adapted, with permission, from reference 19.

Palatoglossus

The palatoglossus muscle originates in the palatal aponeurosis and inserts onto the base of the tongue, and is innervated by the pharyngeal branch of the vagus nerve. It thus forms the anterior pillar of the palatal arch and, as stated above, pulls the palate down onto the posterior tongue. It may also elevate the base of the tongue. Studies conducted in man suggest that this muscle does have respiratory modulation, generally with an inspiratory phasic activation pattern (165,255). The muscle is more active, with greater inspiratory activation, during nasal than oral ventilation.

At least three studies in awake humans suggest that pulses of negative pressure lead to a rapid activation of this muscle (150, 163, 165). When an inspiratory resistive load is applied, inspiratory activity increases as well (255). In addition, at least one study does indicate that the muscle responds to rising PCO_2 with increasing inspiratory activation (255). Thus, the muscle does have respiratory modulation, even under basal conditions, and responds briskly to all forms of respiratory stimulation.

During NREM sleep, the little data available suggest that palatoglossal activity decreases during stage 2 sleep, but increases back to waking levels during stages 3/4 sleep (252). This is similar to what is described above for the GG muscle and the stage 3/4 effect likely represents a response of the muscle to increasing airway negative pressure and elevated PCO_2 rather than a pure sleep effect. There are no such studies during REM sleep. The ability of this muscle to respond

to either negative airway pressure or chemical stimuli during sleep has not been studied in either animals or man.

Palatopharyngeus

The palatopharyngeus muscle originates in the soft palate and inserts into the lateral pharyngeal wall and, along with the stylopharyngeus, onto the thyroid cartilage. The muscle is innervated by the pharyngeal branch of the vagus nerve. It is believed to lift the pharyngeal walls and may pull the soft palate down toward the tongue. There is very little information available about the respiratory function of this muscle. However, one study in humans (obstructive apnea patients) does indicate that this muscle has inspiratory activation under basal conditions with greater activity supine than in the erect posture and during nasal as opposed to oral breathing (162). The muscle also increased its activity in response to graded increments in negative airway pressure, particularly when applied through the mouth. However, the impact of other respiratory stimuli and sleep effects on the activity of this muscle has not been studied.

Levator palatini

The levator palatini muscle, which is innervated by the glossopharyngeal nerve, extends bilaterally from the temporal bone of the skull to the palatal aponeurosis, ultimately progressing to the midline. Thus, when activated, it elevates the palate and can completely close off the nasal airway from the lower airway that occurs during oral breathing, speech, and swallowing. The relatively small data set addressing its respiratory role in man suggests that the muscle does have respiratory modulation (163, 165, 252, 255). In one study, all participants demonstrated inspiratory phasic activation of the levator palatini (165) while in two studies approximately half had inspiratory activation and the other half primarily expiratory activity (254, 255). In both studies, muscle activity (respiratory and tonic) was greater during oral than nasal ventilation (165, 255). Animal studies have demonstrated inspiratory and expiratory phasic activity in this muscle (263, 264). In addition, in dogs phasic respiratory modulation was also present when the animal was breathing completely through a tracheostomy, indicating respiratory influences on muscle activation apart from local negative pressure reflexes (263, 264). Thus, the activation of the levator palatini appears to be quite variable across subjects.

Currently available data also suggest that the muscle can respond to respiratory stimuli. Both inspiratory resistive loading and elevations in PCO_2 led to greater activity in this muscle, again primarily during oral breathing (255). Pulses of negative pressure also induced increased muscle activation (163, 165). Animal studies support this responsiveness of the muscle to respiratory stimuli (263, 264). Finally, one study examined the effect of NREM sleep on the levator palatini and reported decreased inspiratory phasic and expiratory tonic activity (252). No data during REM sleep have been reported.

Tensor palatini

The TP muscle, innervated by the trigeminal nerve, originates on a variable combination of the cranial base and the auditory tube cartilage. The muscle fibers converge on a tendinous plate that ultimately becomes a common tendon. This tendon rounds the pterygoid hamulus and then inserts on the palatal aponeurosis (3). Thus, contraction of this muscle can both influence auditory tube patency and stiffen the palate, thereby potentially improving retropalatal airway patency.

Most evidence, particularly in humans, suggests that this muscle does not have respiratory modulation in the resting state, but is a tonic muscle (128, 252, 253). However, results from dogs indicate that the muscle can have both inspiratory and expiratory phasic activation (5). Human data do demonstrate an increase in muscle activity in response to pulses of negative pressure (278), but a variable response to elevations in PCO_2 (128). These observations are supported in part by animal data that indicate muscle responsiveness to both negative pressure (5) and hypoxic hypercapnia (263). Stimulation of the TP in the isolated upper airway of the cat increased airflow and reduced (more negative) the critical closing pressure, suggesting an improvement in airway patency and a reduction in collapsibility (153).

Human data are quite consistent in showing a decrement in TP muscle activity during NREM sleep (252, 253, 289). The decrement is progressive, with time asleep reaching a level in at least one study of approximately 25% of the waking level during stages 3/4 sleep (253). When all respiratory inputs to the muscles are maximally reduced or eliminated (nasal ventilation with EPAP), there is still a decrement in TP activity from wakefulness to NREM sleep without further decrement in REM sleep (133). Thus, wakefulness itself activated this muscle. In addition, the muscle does not seem to respond as readily during NREM sleep as the GG (see above) to endogenous increments in pharyngeal negative pressure (more negative) and rising PCO_2 (138, 141). When pulses of negative pressure are applied to the airway, the response of the TP during NREM sleep is also reduced when compared to wakefulness (278).

Musculus uvula

The musculus uvula, in man, extends from the palatal aponeurosis into the uvula and is innervated by the pharyngeal branch of the vagus nerve. The precise function of this muscle is unclear at this time. It is argued that it can influence the shape of the uvula and soft palate, thereby improving velopharyngeal closure during oral breathing, swallowing, etc. (121). Others have argued for a role in speech that may be a similar function. Data from dogs suggest that this muscle can have inspiratory and also possibly expiratory phasic activity on a background of tonic activation (263, 264). These same studies suggest the muscle can respond to both negative pressure and hypoxic hypercapnia (263, 264). The only assessment of respiratory activation in man, published only in abstract form,

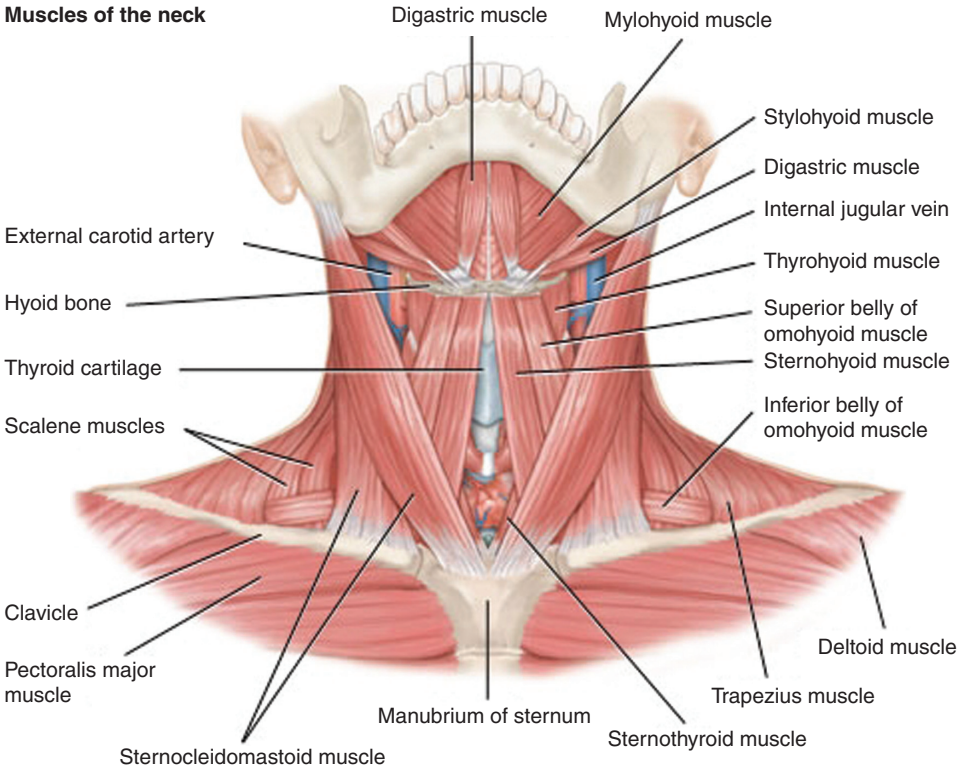

Figure 10 Depicted in this figure are the multiple muscles that attach to the hyoid bone and influence its position. Adapted, with permission, from reference 67.

suggests a high dependence on breathing route (204). The muscle is quiet during nasal breathing, more active with naso-oral breathing, and most active during pure oral breathing. The activation pattern varied between subjects, with some demonstrating inspiratory phasic activation, others primarily expiratory activity, and still others only tonic activity (204). No data on activity during sleep are available. Thus, it is unclear if this muscle has a role in maintaining airway patency in man.

Muscles influencing hyoid bone position (Fig. 10)

The hyoid bone sits at the base of the tongue and the movement of this bone can influence the position of the tongue and thus the anterior wall of the pharyngeal airway. Seven muscles attach to the hyoid bone and, in combination, determine its position. The bone is pulled in the anterior direction by the *mylohyoid*, *geniohyoid*, and *digastric* muscles, in the posterior direction by the *stylohyoid*, and in the inferior direction by the *omohyoid*, *sternohyoid*, and the *thyrohyoid* muscles. The activation pattern is known for most of these muscles, but little information about their responsiveness to mechanical and chemical stimuli is available. Very little is known about the influence of sleep on their activation. What is known will be provided below. The muscles will be grouped based on their influence on hyoid position.

Geniohyoid, mylohyoid, and digastric

The geniohyoid is the best studied of these muscles and is innervated by the hypoglossal nerve. Older data suggest that this muscle demonstrates an inspiratory phasic activation pattern under resting conditions in both animals and man (261, 281). However, a recent study suggests this may not be the case (39). Animal data also show a clear increase in geniohyoid EMG activity with increased PCO_2 (39), although one study suggested that this was not always associated with muscle shortening (39). Data from cats indicates that increases in upper airway volume are associated with geniohyoid shortening and vice versa (265). Thus, the geniohyoid is likely a respiratory modulated muscle that can increase airway size and patency. Studies in man also show an inspiratory phasic activation pattern with decreased muscle activity during both NREM and REM sleep (281). The loss of geniohyoid EMG during sleep was primarily a product of decrements in tonic activation with preserved inspiratory activity. There was a loose relationship between loss of geniohyoid activity and increases in upper airway resistance between wakefulness and sleep (281). Finally, electrical stimulation of the geniohyoid muscle reduced airflow resistance in the upper airway of the dog (32), but had minimal effects in humans (212).

The mylohoid muscle in rabbits responded to negative airway pressure and elevated airflow resistance with increased activity (239). No other data assessing respiratory activation

or sleep effects on the mylohyoid muscle are available in man or animals.

One study reported no respiratory modulation of the digastric muscle in anesthetized rabbits (206). Another in humans found no activity under resting conditions for the digastric, but considerable activation when the mandible was lowered (44). No other data regarding respiratory modulation or sleep effects on this muscle could be found.

Stylohyoid

This muscle is innervated by the facial nerve. However, very little data are available regarding the respiratory control of this muscle or sleep affects on its activation. One study in rabbits did suggest there was no respiratory modulation of this muscle under resting, anesthetized conditions (206).

Omohyoid, sternohyoid, and thyrohyoid

There is not a great deal of information about any of these muscles. The best studied is probably the sternohyoid (innervated by the facial nerve): this muscle has phasic inspiratory activity in anesthetized dogs that increases with elevations in PCO_2 (261). However, in another study of dogs, respiratory activity was not present until the animals were made severely hypoxic (66). One study assessed sternohyoid muscle length under a variety of condition and reported actual muscle lengthening in association with hypercapnia-induced increases in muscle activity (39). With increased airway volume, the muscle shortened, suggesting it is a pharyngeal dilator. Finally, electrical stimulation of the sternohyoid had little effect on upper airway resistance in dogs (32).

The thyrohoid muscle has been reported to have phasic inspiratory activity in dogs that increases with elevations in PCO_2 (261). Little additional information is available. Finally, the omohyoid muscle has no activity under resting conditions in man (44) and seems to serve primarily to lower the jaw. However, phasic inspiratory activity of the omohyoid in monkeys could be induced with airway obstruction and hypoxia (66). There are no studies assessing sleep effects on muscle activation for any of these muscles.

Pharyngeal constrictor muscles (Fig. 11)

There are three pharyngeal constrictor muscles, the *superior*, *middle*, and *inferior*. These muscles make up the posterior

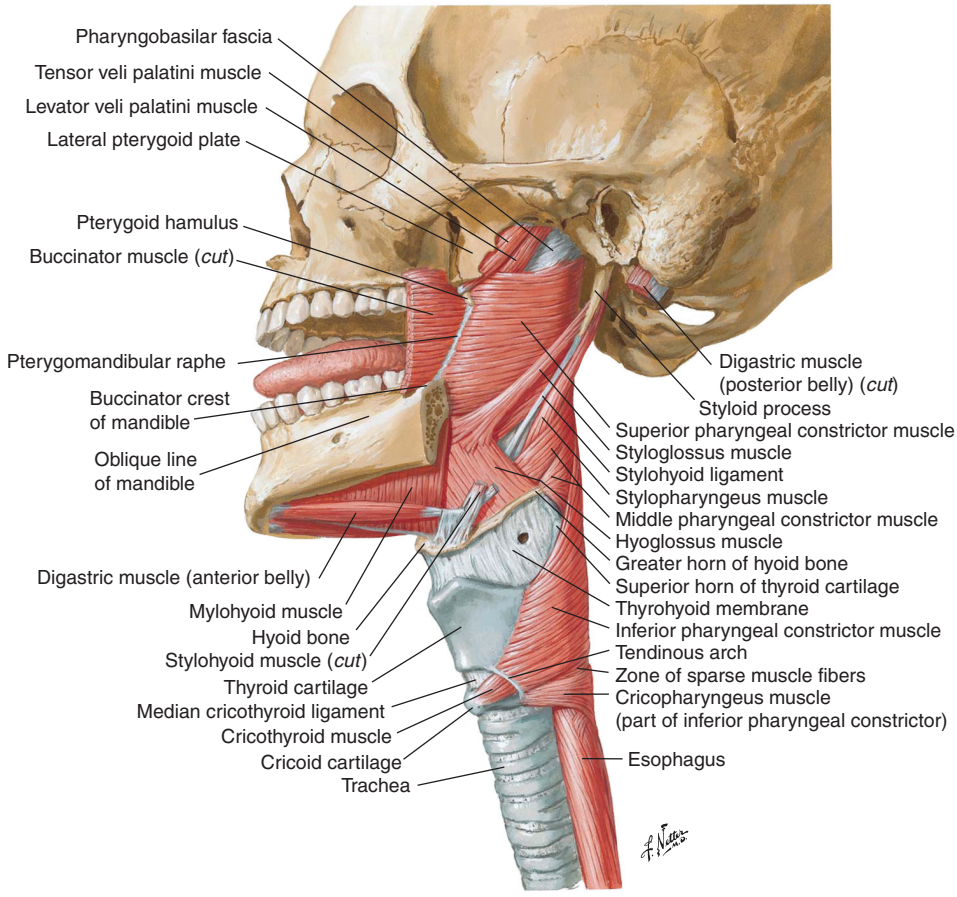

Figure 11 Many upper airway structures are shown on this figure. It is shown here primarily to demonstrate the superior, middle, and inferior constrictor muscles of the pharynx. Adapted, with permission, from reference 167.

and lateral walls of the pharyngeal airway. All three muscles originate in the posterior midline from an aponeurosis, wrap around the airway, and insert onto a variety of structures in the anterior pharynx. The muscles are innervated primarily by branches on the glossopharyngeal and vagus nerves. The primary activity of the muscles is pharyngeal closure during swallowing. However, as will be outlined later, there is reason to believe they may have a respiratory function (maintaining airway patency) as well.

As these muscles behave very similarly, they will be discussed as a single muscle unless otherwise indicated. Studies in both man and animals vary as to whether there is activity, and particularly respiratory activity, present under resting conditions (122,123,124). The predominance of the data suggest little such respiratory activity is present and, when it is observed, that the activity is primarily expiratory, starting in late inspiration and spanning expiration (122,123,124). With respiratory stimulation (hypercapnia or hypoxia), prominent expiratory activity is virtually always observed in both man and animals.

As stated earlier, it is generally believed that the activation of the pharyngeal constrictors tends to close the airway as part of swallowing. However, careful studies by Kuna et al. in cats suggest that at normal to high lung volumes, stimulation of these muscles does indeed reduce pharyngeal airway size (125). However, as lung volume falls below functional residual capacity, constrictor stimulation actually decreases airway compliance, yielding a stiffer, less collapsible airway and in some cases actually dilates the airway (125). Thus, pharyngeal constrictor muscles, particularly at low lung volumes, may actually have a role in maintaining airway patency.

Studies in man during sleep indicated that these muscles are minimally active during NREM sleep and that activity during REM sleep was not related to respiration (123). In addition, during hypocapnia-induced apnea during NREM sleep, there was no increase in muscle activation.

Conclusion

The studies described above suggest that airway patency in both animals and man is significantly influenced by a complex activation of various pharyngeal dilator muscles. These muscles generally increase their activity when respiratory stimuli (increased CO_2 or decreased O_2) are applied and in response to local stimulation, generally negative pressure. During sleep, there are less data, but most information suggests a decrement in muscle activation and responsiveness to chemical and mechanical stimuli, although the muscles clearly can respond to both during NREM sleep. Responsiveness during REM sleep may be further diminished. Thus, the pharyngeal airway is likely somewhat more vulnerable during sleep, particularly REM sleep.

Mechanisms of Pharyngeal Obstruction During Sleep

Pharyngeal anatomy and mechanical properties in the OSA patient

This topic will be addressed in great detail in another review (Strohl and Malhotra). However, airway properties will be discussed here at least superficially, as this topic is highly relevant to the pathogenesis of OSA.

Imaging of the upper airway

Numerous studies over the last 25 to 30 years have assessed the upper airway, comparing patients with OSA to normal controls. The first such study used CT scanning and quantified the size of the airway lumen in the naso-, oro-, and hypopharynx. At all levels, the airway lumen was reported to be smaller in apnea patients than healthy controls and the size of the airway correlated loosely with various measures of apnea severity (83). Since this seminal study, there have been hundreds of papers addressing this question using a number of different imaging techniques and quantifying anatomy and airway size in quite different ways. To create some order in reviewing this literature, these papers will be grouped based on specific observations regarding pharyngeal airway anatomy and physiology.

Airway lumen

Size

Virtually all studies that have compared, during wakefulness, the size of the upper airway lumen between OSA patients and normal controls, including the original study referred to above, have reported a smaller airway in the apnea patients (101, 215, 216, 218, 246). This observation is consistent across imaging methodologies [magnetic resonance imaging (MRI), computed tomography (CT), fluoroscopy, acoustic reflection, cephalometry, and endoscopy]. When such assessments are possible, the difference in size is generally greater in the retropalatal region than elsewhere, although the retroglossal area tends to be smaller as well. This is the case whether the assessment is done in two or three dimensions (2D or 3D) (MRI). The smallest airway luminal size in both apnea patients and controls has virtually always been found to be in the retropalatal area (216). Finally, when the airway is imaged rapidly across the respiratory cycle, the smallest airway luminal size is generally observed at the end of expiration when the pharyngeal dilator muscles are least active and lung volume is at its lowest level (see later) (Fig. 12) (215). This is the case in OSA patients and controls when imaged during wakefulness. In apnea patients, there is a progressive decrease in the size of the retropalatal airway at the end of expiration leading up to the actual apnea. Thus, in frank apneas, the airway likely closes at end expiration.

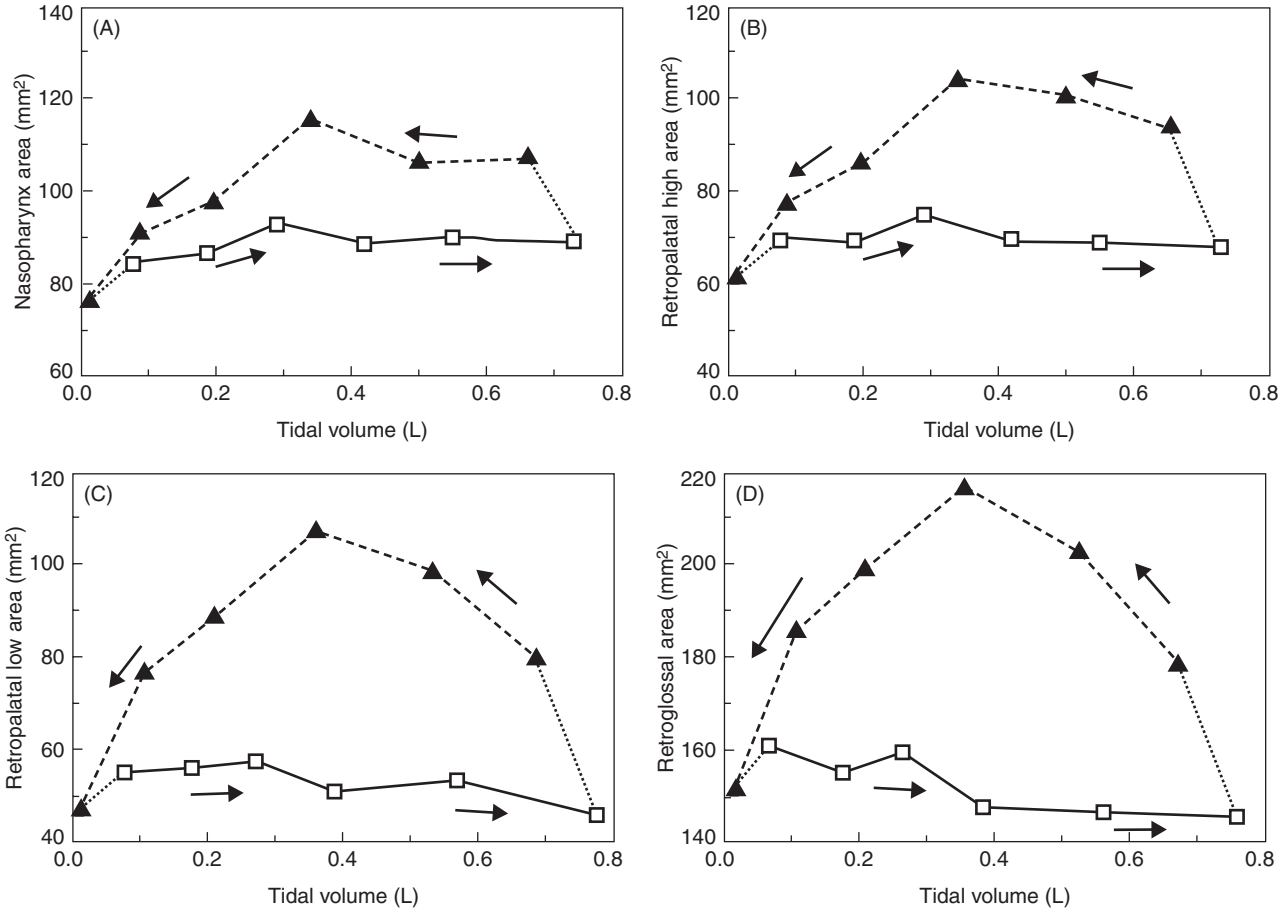

Figure 12 Upper airway cross-sectional area plotted as a function of tidal volume in an apneic patient over four anatomic levels. In this apneic subject, the upper airway at all four anatomic levels enlarges in early inspiration and then remains relatively constant during the rest of inspiration, enlarges significantly in early expiration, and then narrows significantly toward the end of expiration. (A) Nasopharynx, (B) retropalatal high, (C) retropalatal low, and (D) retroglossal. (*Solid line with open squares* = inspiration, *dashed line with closed triangles* = expiration, *dotted line* = extrapolation between end of inspiration and the beginning of expiration, and between end of expiration and the beginning of inspiration.) Adapted, with permission, from reference 215.

For many years, it was argued that any assessment of airway size made during wakefulness was fundamentally flawed, as the muscle activity present in waking subjects could influence airway luminal dimensions. Thus, any reduction in airway size could be a product of pure anatomy or diminished muscle activation. To address this problem, Isono et al. (101) assessed airway characteristics using endoscopy while the subjects were completely paralyzed. Thus, any difference in muscle activation was eliminated. Using this technique they created airway area-pressure plots and observed the airway size of the apnea patient to be smaller than that of the controls at virtually all airway pressures. They made two other observations of note. First, the closing pressure of the airway (the pressure at which the airway closed completely) tended to be higher (less negative or actually positive) in apnea patients than controls, with most OSA patients having a positive closing pressure (Fig. 13) (101). In addition, the velopharynx (the area behind the palate) was consistently smaller than the oropharynx in both patients and controls. Therefore, this study left little doubt that most apnea patients have an anatomically small pharyngeal airway. However, it should be pointed out that there was overlap between groups in the closing pressure, with some controls having a higher closing pressure than patients with OSA. Thus, anatomy is not likely the entire explanation for apnea pathogenesis.

Shape

A number of the studies described earlier assessed not only airway size, but airway shape as swell. These reports were consistent in the observation that apnea patients tend to have an airway that is longer in the anterior-posterior (AP) dimension, while healthy controls have an airway that is oriented in the lateral direction (129, 205, 216). This would lead to the conclusion, as will be discussed later, that the lateral walls of the airway are thicker in the apnea patients (216). It has also been argued that an AP-oriented airway will dilate poorly in response to dilator muscle contraction,

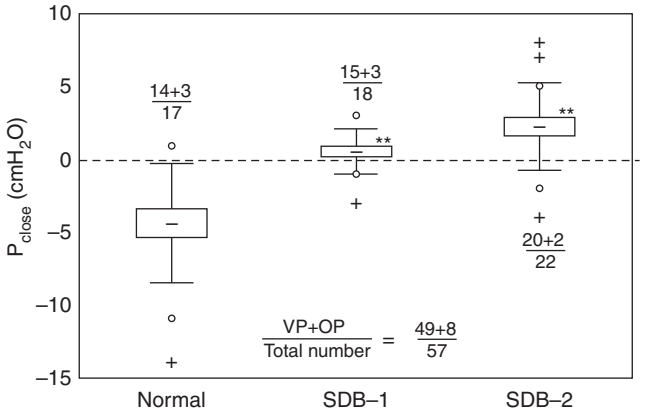

Figure 13 Box plots illustrating observed closing pressures (Pc). Distribution of sites of primary closure was provided for each of three groups: normal, sleep-disordered breathing (SDB)-1, and SDB-2. Mean values are indicated by horizontal bar within each box; bars above and below each box represent SE. Ends of vertical lines denote SD. O or + symbols, outliers. VP, velopharynx; OP, oropharynx. $^{**}P < 0.01$ versus normal group. Adapted, with permission, from reference 101.

particularly to muscles such as the GG that have an AP orientation themselves (129).

Length

Based on simple mechanical principles, a longer airway will be more collapsible than a shorter one assuming both are similarly tethered. Thus, increased airway length could predispose an individual to the development of sleep apnea. There are now a number of papers indicating that apnea patients, as a group, do have a longer airway, generally measured from the hard palate to the epiglottis (140, 180). In addition, modeling studies have confirmed this concept, demonstrating greater collapsibility as the airway lengthens (140). Finally, women have been reported to have a shorter airway, corrected for height, than men that could protect them from the development of OSA (140).

Soft tissue around the airway

It should first be stated that the total volume (assessed by MRI) of all of the tissue (listed individually below) surrounding the airway is greater in patients with sleep apnea than normal control subjects. As this total volume increases, the risk of sleep apnea increases. Hereafter, the individual components of this tissue will be the focus of the discussion.

Lateral pharyngeal walls

Schwab et al. have provided convincing evidence from MRI studies that the lateral pharyngeal walls of the apnea patient are thicker (in 2D) and have greater volume (in 3D) than those of normal controls (216, 218). This is the case despite the fact that the distance between the mandibular rami at the level of the smallest airway was similar between the two groups, as was the size of the parapharyngeal fat pad. Thus, there is more nonfat, soft tissue in the lateral pharyngeal walls of the OSA patients than the controls. This is the likely explanation for the AP-oriented airway lumen in the apnea patient as described earlier (129). The strongest predictor of the presence of sleep apnea of all airway anatomic measurements was the total volume of the lateral pharyngeal walls (217).

These lateral pharyngeal walls are composed of primarily muscle, but also fat (parapharyngeal fat pads, see below) and lymphoid tissue. The aforementioned observations would suggest that there is simply more tissue in these lateral walls of patients versus controls. An alternative explanation would be that AP collapse isolated to the lateral margins of the pharyngeal airway could give the appearance of thick lateral walls. This folding of tissue at the lateral edge of the pharyngeal airway lumen could appear to be thickening of the lateral walls when this is not strictly the case. When CPAP is applied to the airway, the lateral walls thin considerably, which may be more compatible with the opening of collapsed tissue at the lateral margin of the airway than a highly compliant lateral wall (217). However, this issue has not been completely resolved.

Soft palate

Most evidence suggests that the size of the soft palate is increased in patients with OSA. In 2D assessments, the soft palate area and length (103) were greater in the apnea patients, while the width or thickness of the soft palate was similar between groups. Subsequent studies that quantified tissue volume (3D) also reported a larger soft palate in the apnea patients than the nonapneic controls (216, 218).

Tongue

The area of the tongue, from 2D assessments, is consistently reported to be larger in apnea patients than healthy controls. This is also the case when tongue volume (3D) is measured (216, 218). Total tongue volume was a strong independent predictor of the presence of sleep apnea in multivariate analysis.

Parapharyngeal fat pads

The fat pads that comprise a portion of the lateral pharyngeal walls, when examined in their entirety using 2D methodologies, are generally larger in OSA patients than normal controls. This is the case when volumetric assessments are made as well (216, 218).

Bony structure surrounding the airway

A number of studies suggest that craniofacial structure may also importantly predispose some individuals to the development of OSA (230, 248, 270). The most consistent

observations when apnea patients are compared to normal controls indicate that the apnea patients have:

- Maxilla: Shorter with a narrow, tapered arch.
- Mandible: Smaller mandibular enclosure and retroposition of the mandible.
- Hyoid: Greater inferior displacement from the mandibular plane.

Thus, in most OSA patients, the passive pharyngeal airway size is a product of two independent variables. One would be the size of the bony enclosure surrounding the airway, as described earlier, and the other would be the quantity of soft tissue placed in this enclosure (270). If the enclosure is small relative to the quantity of tissue it must contain, then airway compromise is likely. Shelton et al. first made this observation, reporting that apnea patients had a smaller "area enclosed by the mandibular ramus" and a shorter distance from the incisors to the posterior border of the ramus of the mandible (230). This would suggest that the space inside the mandible is small in some apnea patients. Smaller maxillas have been demonstrated as well.

The degree to which soft tissue versus bony enclosure influences the development of OSA seems to vary across ethnic lines (248) In Caucasians, the anatomically small pharyngeal airway of the apnea patient seems to be a product of both increased soft tissue, primarily from obesity, and some reduction in the bony enclosure. In African-Americans (41) craniofacial structure seems to play little role in the development of sleep apnea, with increased soft tissue being the primary abnormality. Finally, in Asians, in whom obesity is less common, similar apnea prevalences have been reported; the bony enclosure seems to be reduced in size with a smaller, retropositioned mandible and reduced maxilla as well. However, in all groups apnea becomes more severe as BMI increases.

Other structural influences on upper airway anatomy/size

Blood volume

Several recent studies suggest that the accumulation of blood/fluid in the vessels and tissues of the neck may contribute to upper airway compromise during sleep (48,198-200, 307). This was first accomplished in normal subjects by compressing the lower extremities and measuring airflow resistance in the pharyngeal airway during wakefulness. A small, but highly consistent increase in airflow resistance and neck circumference was observed with this compression, which forced blood/fluid out of the lower extremities and into the circulation (48). They next measured lower extremity edema prior to sleep and the transudation of fluid out of the lower extremities and into the circulation. They observed a strong correlation between the amount of fluid exiting the lower extremity and the observed AHI that night (200). There was also a significant increase in neck circumference following the movement of fluid from the legs. These two studies suggest that in some patients, movement of peripheral edema at night from the extra- to the intravascular space may lead to accumulation of fluid in the neck with subsequent compromise of pharyngeal patency. Finally, several studies suggest that the use of compression stockings during the day may actually reduce apnea severity in individuals who are sedentary (198) or have venous insufficiency (199).

Airway edema and inflammation

A number of studies, based primarily on uvula and soft palate tissue (6, 37, 185, 222) obtained from snorers and OSA patients and autopsy material from nonapnea patients, indicate that there is increased inflammation in the upper airway of sleep apnea patients. This is certainly the case in the mucosa, where leukocyte infiltration and edema of the lamina propria have been observed by a number of investigators. Structural changes in the mucosa have also been reported such as acanthosis overlying the epithelium and loss of connective tissue papillae (185). More recently, similar inflammation has actually been observed in the muscle layer of the soft palate as well (37). Such inflammatory changes could certainly lead to airway edema, which could be another factor contributing to decreased airway size. Potentially more important, such inflammation could affect both afferent and efferent neural function in the airway. This possibility will be addressed later in the review.

The studies described earlier indicate that there is edema of the upper airway using histological techniques. Studies conducted in whole animals (cats) (268) and humans (269) indicate that the application of vasoconstrictor agents to the pharyngeal mucosa can, in animals, make opening and closing pressures in the airway more negative (less collapsible airway) and in humans decrease pharyngeal airflow resistance. In animals vasodilators led to a reduction in airway cross sectional area and volume per MRI (268). Thus, airway edema can affect the size of the pharyngeal airway lumen.

Lung volume effects

Although it could be argued that changes in lung volume do not structurally affect the pharyngeal airway, this seemed the most appropriate place to address this literature. In the 1980s and early 1990s, a literature began to emerge that rising lung volume increased the size of the pharyngeal airway. In animals this was convincingly demonstrated by Van de Graff (260), as was the concept that this change was mediated by longitudinal traction on the structures of the pharyngeal airway. Studies in humans at about the same time (38) demonstrated that volitional changes in lung volume during wakefulness had large effects on the size of the upper airway as measured by acoustic reflection. In addition, several studies

reported convincing falls in functional residual capacity during sleep (14, 94). However, it was argued that such changes in airway size could be mediated by either longitudinal traction or increased upper airway dilator muscle activity.

Subsequent studies by Heinzer et al. (86) were the first to actually manipulate lung volume during sleep and observe changes in measures of airway collapsibility in patients with OSA. These investigators altered lung volume by changing extrathoracic pressure in an iron lung while measuring both changes in lung volume (magnetometers) and upper airway collapsibility (CPAP pressure required to prevent the development of flow limitation). At baseline, 11.9 cmH2O was required to prevent flow limitation. This decreased to 4.8 cmH2O when end-expiratory lung volume was increased by 1035 mL and increased to 17.1 cmH2O when lung volume was reduced 732 mL. Heinzer et al. (86) went on to demonstrate that increases in lung volume could substantially reduce the AHI in patients with severe OSA. However, this effect has not always been observed (87).

Thus, the preponderance of the data suggests that the decreases in lung volume that occur during sleep may render the pharyngeal airway more collapsible than was the case at higher lung volume. In addition, passive increases in lung volume during NREM sleep reduce airway collapsibility and the severity of sleep apnea in patients with OSA.

Conclusions

The data outlined above strongly suggest that OSA patients have an anatomically small pharyngeal airway. This compromised airway may be the product of excess tissue, which often results from obesity, or a small bony enclosure with a normal tissue load. That being said, it should be recognized that some patients with sleep apnea have relatively normal upper airway anatomy while some individuals without apnea have an anatomically quite small airway. Thus, other physiologic characteristics, as will be addressed later, likely contribute to the pathophysiology of OSA.

Relation Between Pharyngeal Morphology and Maximum Flow in the Passive Pharynx

An understanding of the mechanical properties of the passive human pharynx is essential to this topic because it is these passive properties that determine whether, and by how much, pharyngeal dilators must be activated to maintain adequate ventilation (297). Except at its extreme upper and lower ends, where it is anchored to bone and cartilage (larynx), respectively, the human pharynx has no rigid support. Accordingly, throughout most of its length its cross-sectional area varies with lumen pressure (100, 101). As indicated earlier, there is much evidence that the airway of OSA patients is, on average, narrower and closes at a higher airway pressure than the airway of patients with minimal or no OSA.

It is intuitively obvious that a narrower pharynx should offer a greater resistance to airflow. However, an increase in resistance would not cause a significant problem if the resistance were fixed. For example, with a normal upper airway resistance of 4 $cmH_2O/L/s$ (e.g. references 7 and 99), inferior pharyngeal pressure need only be –2 cmH_2O to produce an entirely adequate inspiratory flow during sleep of 0.5 L/s. If upper airway resistance were to increase 10-fold (to 40 $cmH_2O/L/s$), but remain fixed, inferior pharyngeal pressure would have to decrease to –20 cmH_2O to achieve a near normal flow. Such negative values can readily be achieved during sleep through increased diaphragmatic activity in response to mild changes in blood gas tensions. In fact, patients with OSA often develop much more negative intrathoracic pressures during sleep (e.g. references 25 and 114), but to no avail. Therefore, the problem in these patients is not the high resistance but the fact that airflow cannot be increased through increases in inspiratory effort (i.e. flow limitation).

Mechanism of flow limitation

The pharynx is a collapsible tube the dimensions of which change with luminal pressure (Fig. 14A) (101). The relation between driving pressure and flow in collapsible tubes does not follow simple Ohmic principles (flow = $\Delta P/R$). This is because as more negative pressure is applied at the downstream end of the tube, the pressure within the lumen becomes more negative. The tube decreases its dimensions and its resistance increases. Up to a certain negative downstream pressure the increase in resistance is not enough to offset the increase in ΔP, and flow can increase. However, at some negative pressure value, the increase in resistance cancels out the increase in ΔP. Beyond this point further increases in ΔP no longer result in increased flow [flow limitation; $\dot{V}_{MAX}$ (e.g. references 99 and 237) and in fact may paradoxically result in less flow [negative effort dependence (99)]. Negative effort dependence is frequently seen during obstructive hypopneas as a progressive reduction in flow during the inspiratory phase of individual breaths, even though the driving pressure for airflow is increasing (51, 92) [Figure 15 from reference (92)].

That flow becomes independent of, or negatively affected by, effort has two important implications. First, once an obstructive event develops flow can increase only through increased activity of the pharyngeal dilators. Second, the ventilatory response to the changes in PCO_2 and PO_2 is no longer determined by the response of pump muscles but by the response of pharyngeal dilators to these and other stimuli. These two conclusions emphasize the importance of dilator responses in determining the outcome of the obstructive event.

Figure 14A illustrates the spectrum of pressure-area relations of the *passive* pharynx observed in different subjects at the pharyngeal level associated with minimum dimensions [oro- or velo-pharynx; constructed from data in reference (101)]. Within each subject, there is a pressure level at

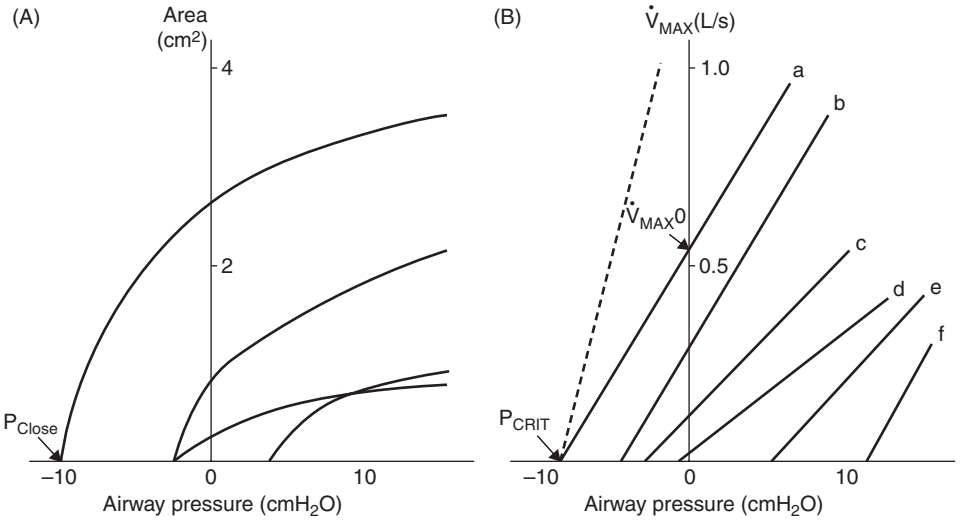

Figure 14 (A) Relation between external airway pressure and minimum pharyngeal cross-sectional area in four subjects, representing the spectrum of passive mechanical properties of the pharynx. P_{Close}, pressure at which the pharynx is closed. Constructed, with permission, from data in reference 101. (B) Relation between external airway pressure and maximum flow conducted by the upper airway ($\dot{V}_{MAX}$). Lines A to F provide the spectrum seen in patients with obstructive sleep disorders (constructed, with permission, from data in reference 297). The dashed line represents a subject who would have no obstructive abnormality during sleep. $\dot{V}_{MAX}0$, maximum flow that can be conducted in the absence of pharyngeal dilator activity in the subject breathing with no external pressure applied. Modified, with permission, from reference 297.

which the passive airway is completely closed (P_{Close}) and that P_{Close} varies considerably among subjects [up to 15 cmH_2O (237)]. Above P_{Close}, the pressure-area relation is nonlinear with the slope (ΔArea/ΔP; airway compliance), decreasing as area increases. At high pressures, the pharynx becomes very stiff. Both maximum area and the shape of the relation (how compliance changes with airway pressure) vary considerably among different individuals and in the same individual at different pharyngeal levels (101). The structural bases for these differences have been discussed in detail in the preceding sections.

As may be expected, the maximum flow that can be conducted through a collapsible tube segment ($\dot{V}_{MAX}$) increases with tube area (A) (a wider tube has lower resistance) and decreases with tube compliance ($\Delta A/\Delta P$), because a more compliant tube narrows more in response to a given reduction in intraluminal pressure. The actual relation between $\dot{V}_{MAX}$, area, and compliance is given by (55, 286):

$$\dot{V}_{MAX} = A^*[A/(\rho(\Delta A/\Delta P))]^{0.5} \quad (1)$$

where ρ is gas density, which is a constant. It is clear that the maximum flow that can be conducted by a pharyngeal segment varies considerably depending on where that segment is operating within its pressure-area relation.

The pharynx can be viewed as consisting of several compliant segments in series, with each segment having its own pressure-area relationship. In the presence of flow, there is a longitudinal pressure gradient along the length of the pharynx so that not every segment is subjected to the same pressure. Accordingly, different segments operate at different points in their pressure-area relation. However, flow rate is the same in all segments. Thus, at any point in time flow in one segment may be far less than this segment can conduct based on its current area and compliance, whereas in another segment flow may be at, or close to, that segment's $\dot{V}_{MAX}$. As effort increases and intraluminal pressure decreases, all segments undergo a reduction in area and an increase in compliance. Hence, the maximum flow that can be conducted decreases in all segments. So long as actual flow is below the $\dot{V}_{MAX}$ of all segments, flow can increase with increasing effort. However, as soon as flow reaches $\dot{V}_{MAX}$ of one (any) segment it can no longer increase in that segment and, because the segments are in series, that segment limits the flow in the entire pharynx (choke point). From that point on, increasing effort simply results in further reduction in pressure and more collapse in the segments downstream from the choke point. Hence, with much increase in effort, more than one pharyngeal segment can be observed to collapse. When multiple segments collapse during inspiration the most upstream segment is the main culprit.

Whereas the aforementioned scenario readily explains flow limitation, negative effort dependence (flow decreasing as effort increases) is more difficult to explain. In theory, once a segment limits flow, further reduction in downstream pressure is not transmitted to the upstream segment (Waterfall concept) so that the dimensions of the upstream segment should not change and the pressure drop from the external airway to the choke point should, as a result, not change. $\dot{V}_{MAX}$ should remain the same because the pressure at the

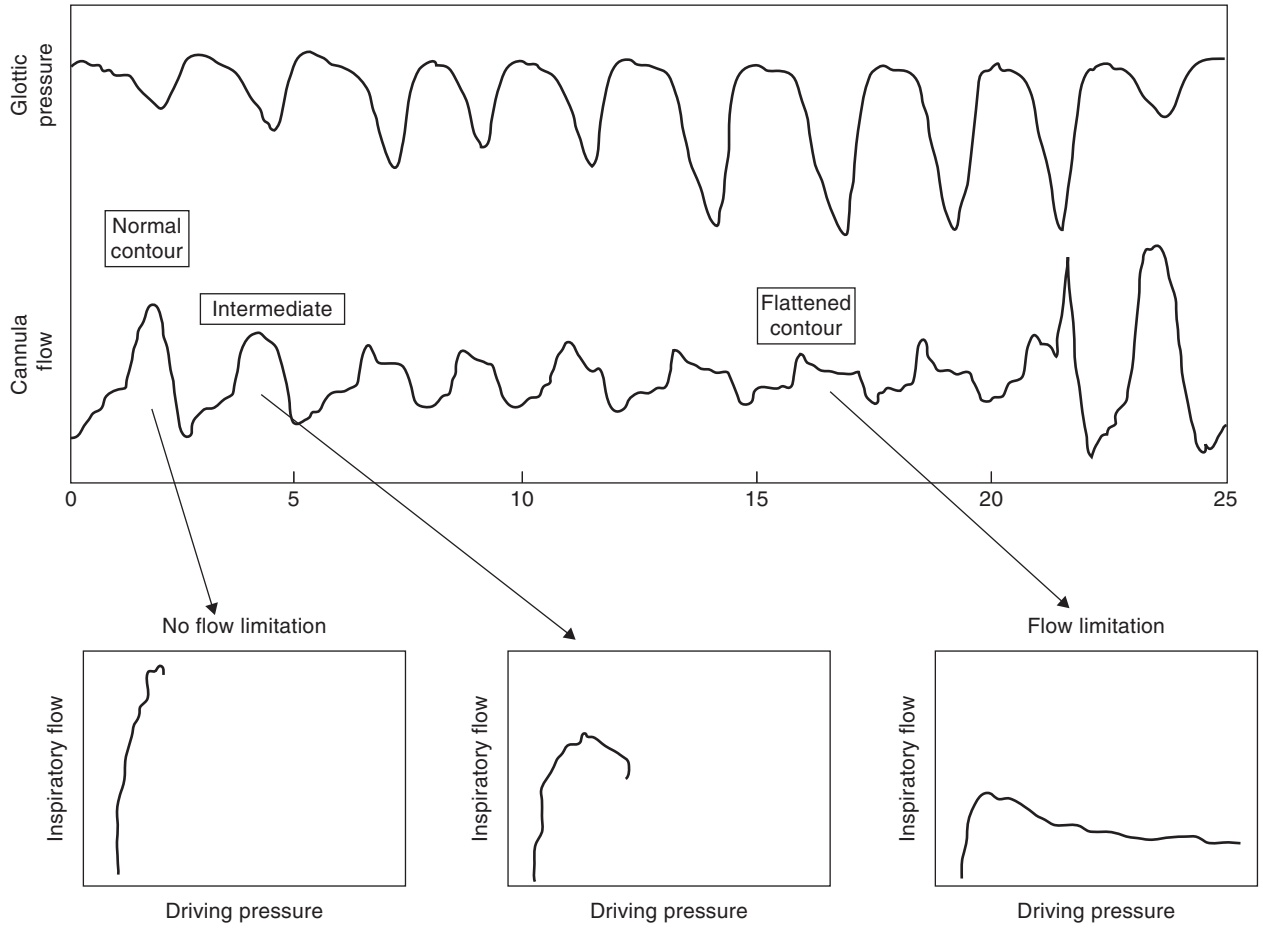

Figure 15 Pressure/flow relationships during a single respiratory event. The x-axis shows time in seconds. Breaths with normal, intermediate, and flattened flow contours are labeled and a plot of the driving pressure/flow relationship is shown. As illustrated in the third small panel below, flow within each of the inspiratory phases beyond 5 s decreases as glottic pressure becomes more negative. This negative effort dependence is seen in some, but not all, flow limited breaths. Adapted, with permission, from reference 92.

choke point (and hence its area and compliance) should not be affected. However, since the pharynx is one long tube, it is possible that the collapse of the downstream segments with increasing effort may indirectly result in reduction of the area of the upstream segments through mechanical interdependence. If so, upstream resistance may increase with increasing effort, resulting in a larger pressure drop from the external airway to the choke point. The lower pressure at the choke point would necessarily cause further reduction in that segment's $\dot{V}_{MAX}$. The magnitude of negative effort dependence appears to vary considerably among different subjects (99)

Relation Between Airway Pressure and Maximum Flow

The mechanical properties of the pharynx are most frequently evaluated by measuring the maximum flow at different external airway pressure values (34, 182, 220). In practice, this is done by placing the subject on optimal CPAP and reducing the pressure in steps until the airway closes completely (i.e. flow = 0). The pressure at which the airway closes using this technique is referred to as P_{CRIT} to distinguish it from other methods of measuring closing pressure. At pressures above P_{CRIT}, there is a pressure range over which flow is limited. At still higher pressures, there is no evidence of flow limitation. The mechanical properties of the pharynx are assessed from the pressure-flow relation in the pressure range where flow is limited. A complete definition of this relation in a wide spectrum of subjects requires the use of devices that can deliver negative as well as positive pressure. Because such devices are not readily accessible, most investigators currently use positive pressure devices. Where P_{CRIT} is greater than 0, the entire relation can be defined. Where P_{CRIT} is less than 0 but there is flow limitation at pressures greater than 0, the P_{CRIT} value can be found by back extrapolation or, alternatively, $\dot{V}_{MAX}$ at an airway pressure near zero ($\dot{V}_{MAX}0$) is reported instead of P_{CRIT} (e.g. reference 292; Fig. 14B).

Flow-limited breaths can be most confidently identified by measuring pharyngeal or esophageal pressure and noting that inspiratory flow fails to increase or actually decreases as pharyngeal pressure becomes more negative during the

breath's inspiratory phase (Fig. 15). However, this invasive procedure is not practical for widespread use. It is now acceptable to identify flow limitation from characteristic flow contours (53, 92, 159).

Early determinations of this relation were made by measuring $\dot{V}_{MAX}$ at different levels of constant sustained airway pressure (76, 227, 237). Because compensatory mechanisms were allowed to evolve at each pressure level before $\dot{V}_{MAX}$ was measured, the reported P_{AW} -$\dot{V}_{MAX}$ relation did not characterize the passive pharynx but, rather, the combined passive and active properties of the pharynx. Therefore, such measurements could not be used to identify the separate roles played by passive (i.e. structural) properties and control mechanisms in the pathogenesis of OSA. More recently, measurement of $\dot{V}_{MAX}$ during the first few breaths after a reduction of CPAP (dial down) has been used to advantage to determine the *passive* mechanical properties of the pharynx (34, 182, 220, 292, 300). This approach is based on the observations that dilator activity is minimal on optimal CPAP (127, 157, 244), and remains unchanged for 2 to 3 breaths following reduction of CPAP (127, 191, 220, 244). Thus, by briefly reducing CPAP to different levels and observing $\dot{V}_{MAX}$, one can conveniently estimate the relation between external P_{AW} and $\dot{V}_{MAX}$ in the passive pharynx with reasonable accuracy (191, 220, 292). With such procedures, $\dot{V}_{MAX}$ generally decreases slightly over the first few breaths after the dial down (220, 292). The reason for this is not clear. It may be due to continued decrease in lung volume (220), or to visco-elastic behavior of the pharynx following acute reduction of CPAP [stress recovery; (292)]. To mitigate the effect of these phenomena, it is preferable to use $\dot{V}_{MAX}$ of the second or third breath to construct the P_{AW} - $\dot{V}_{MAX}$ relationship.

Figure 14B shows the range of the P_{AW} - $\dot{V}_{MAX}$ relations obtained with the brief dial down approach in subjects with OSA of varying severity (220, 292). Consistent with endoscopic observations in the passive pharynx [e.g. Figure 14A (101)] there is a pressure at which the airway closes (P_{CRIT}) and this pressure varies considerably among subjects, from highly negative to highly positive. Unlike the nonlinear pressure-area relation above P_{CLOSE} (Fig. 14A), the P_{AW} - $\dot{V}_{MAX}$ relation is nearly linear over the flow range that is relevant to sleep (Fig. 14B). Thus, the passive mechanical properties of an individual patient can now be readily determined during routine sleep studies and can be simply described by two values, the intercept and the slope.

Some investigators have interpreted the linear P_{AW} - $\dot{V}_{MAX}$ relation as reflecting a Starling resistor-like behavior of the pharynx (e.g. references 236 and 237). Further, the slope of the linear P_{AW} - $\dot{V}_{MAX}$ relation is considered to reflect the conductance of the upstream segment and, by extension, the inverse of the slope is used by these authors to estimate the resistance of the upstream segment [R_{US}, (76, 227, 236, 237)]. However, Younes has contended that the Starling resistor model is inappropriate for pharyngeal flow limitation (see reference 297 for an alternate explanation of the P_{AW} - $\dot{V}_{MAX}$ relation]. It should be noted that the experimentally determined inverse slope of the P_{AW} - $\dot{V}_{MAX}$ relation (25 $cmH_2O/L/s$ (34, 220, 292); range 10 to 62 (292), is an order of magnitude greater than the directly measured resistance of the nose/naso-pharynx (e.g. references 7 and 99). Thus, the use of the inverse slope to estimate naso-pharyngeal resistance is not advisable.

Relation Between Passive Mechanics of the Pharynx and Polysomnographic Severity of OSA

An important question in the pathogenesis of OSA is the extent to which OSA severity is related to structural abnormalities versus abnormalities in the control mechanisms that determine how the subject responds to the structural abnormalities. As indicated earlier, there was considerable overlap in the endoscopically determined P_{CLOSE} among patients with mild, moderate, and severe OSA [(101); Figure 13]. In fact, the r^2 value for the relation between P_{CLOSE} and the respiratory disturbance index (RDI) was only 0.14 in this study. Kirkness et al. (119) determined the relation between AHI and passive P_{CRIT} in 164 subjects ranging from normal to severe OSA. The correlation coefficient was only 0.46 ($r^2 = 0.21$). Younes (292) obtained the relation between AHI and the $\dot{V}_{MAX}$ observed at near atmospheric pressure [$\dot{V}_{MAX}0$; see Figure 14B for definition] in 82 patients with minimal to severe OSA (Fig. 16). The correlation coefficient was 0.53 ($r^2 = 0.28$). In patients with complete obstruction at atmospheric pressure ($\dot{V}_{MAX}0 = 0$), AHI could be as little as 0 or as high as 160 per hour (Fig. 16). Therefore, it is clear that while structural abnormalities that result in flow limitation or complete obstruction

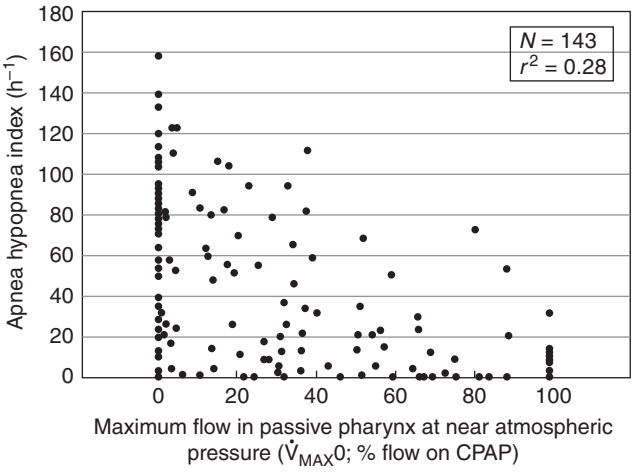

Figure 16 Apnea-hypopnea index (AHI) in 82 patients with varying degrees of passive mechanical abnormalities (maximum flow at near atmospheric pressure). In 61 patients, the relation was determined in two body positions, resulting in 143 patient-position combinations. Note that in patients with complete obstruction at atmospheric pressure (abscissa value = 0) AHI varies between 0 and 160 h^{-1} and that some patients with mild mechanical abnormalities have high AHI values. Adapted, with permission, from reference 292.

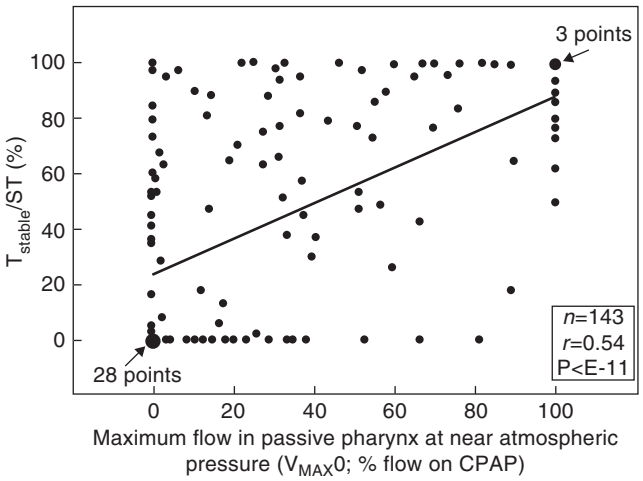

Figure 17 Scatter plot of the relationship between minimum flow observed at near atmospheric pressure and the fraction of sleep time in stable breathing in the same patient-body position combination during polysomnography. Adapted, with permission, from reference 292.

must be present in order for OSA to develop, the manner in which the subject responds to this mechanical challenge is of paramount importance in determining OSA severity.

Another finding that highlights the importance of control mechanisms in determining polysomnographic severity is the recent observation that in the majority of OSA patients there are periods of stable breathing during sleep in the same body position that is associated at other times with recurrent obstructive events [Figure 17 (292)]. In fact, the variability in AHI in a given body position is largely related to the fraction of sleep time spent in stable breathing (292). Figure 18 shows an example. Breathing and sleep suddenly stabilized and remained stable for more than 10 min while the patient was in the same body position. Passive P_{CRIT} was determined in this patient on at least ten occasions throughout the night and was always greater than 0 (average 2.0 cmH_2O), including during periods of slow wave sleep. Thus, the change from cyclic to stable breathing could not have been due to a sudden improvement in pharyngeal mechanics or a change in sleep stage. In further investigations of this phenomenon, Jordan et al. (107) found that these periods of stable breathing are associated with a stable increase in GG activity. Therefore, it is clear that in such patients the neural systems that control dilator muscle activity are capable of mounting an adequate sustained activation of these muscles during sleep (i.e. without the benefit of arousals). To the extent that activation of dilator muscles during sleep involves basic brainstem reflexes and responses that are not likely to be different from time to time during non-REM sleep, the occurrence of periods of recurrent events (OSA) in a patient who also displays periods of stable breathing indicates that the problem during these oscillatory periods is not inadequate responses but exaggerated responses that result in instability. The possible mechanisms

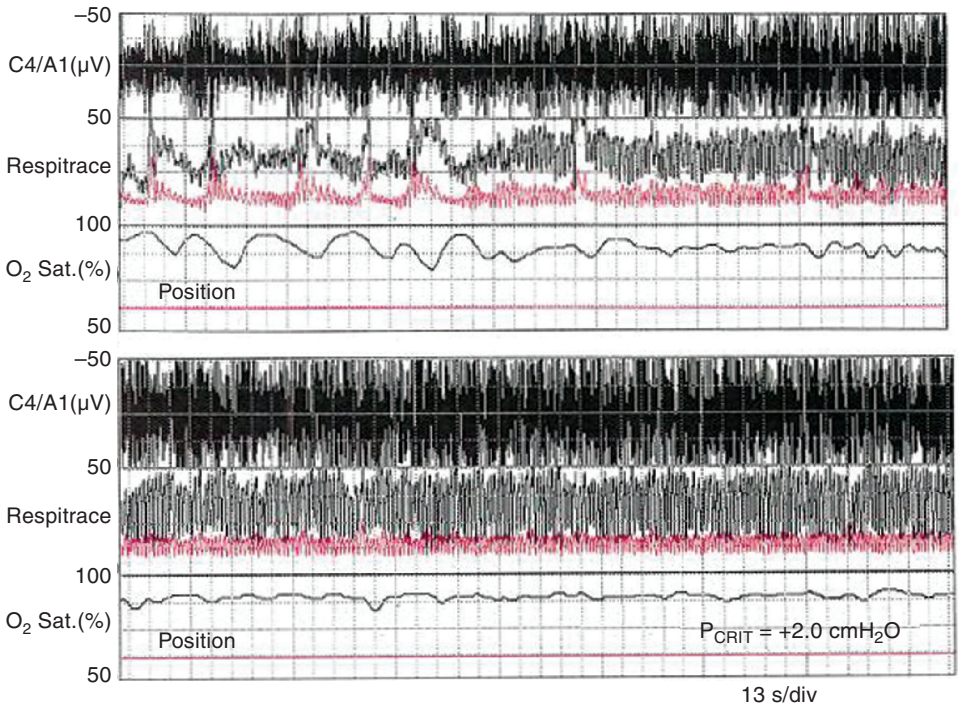

Figure 18 Continuous polysomnography tracings showing spontaneous transition from cyclic obstructions (OSA) to stable breathing in a patient with a highly collapsible pharynx. C4/A1 is the electroencephalogram.

of ventilatory instability in OSA will be discussed at length in the following sections.

Control Mechanisms Available to Compensate for Obstructive Events During Sleep

The control mechanisms that determine how severe OSA will be for a given mechanical severity can be divided into two categories; those that determine the sustainable maximal flow and those that are involved in recruitment of pharyngeal dilators (297). Sustainable Flow is the mean inspiratory flow rate with which blood gas tensions in the steady state do not deteriorate enough to trigger arousal. If sustainable flow can be attained without recruitment of pharyngeal dilators, the major sources of instability are avoided. The main mechanism by which sustainable flow can be achieved without recruitment of pharyngeal dilators is an increase in the inspiratory duty cycle (T_I/T_{TOT}).

Increase in Inspiratory Duty Cycle (T_I/T_{TOT}) (297)

$\dot{V}_E$ is the product of mean inspiratory flow rate (V_T/T_I) and inspiratory duty cycle (T_I/T_{TOT}) (158, 213):

$$\dot{V}_E = 60[V_T/T_I x T_I/T_{TOT}]$$

Thus, for a given mean inspiratory flow (i.e. for a given $\dot{V}_{MAX}$) $\dot{V}_E$ increases in direct proportion to the fraction of time spent in inspiration. It follows that when an obstructive event develops, $\dot{V}_E$ may be increased through an increase in duty cycle. T_I/T_{TOT} increases with sustained flow limitation (106, 213, 243, 267, 284). Figure 19 is an example of how

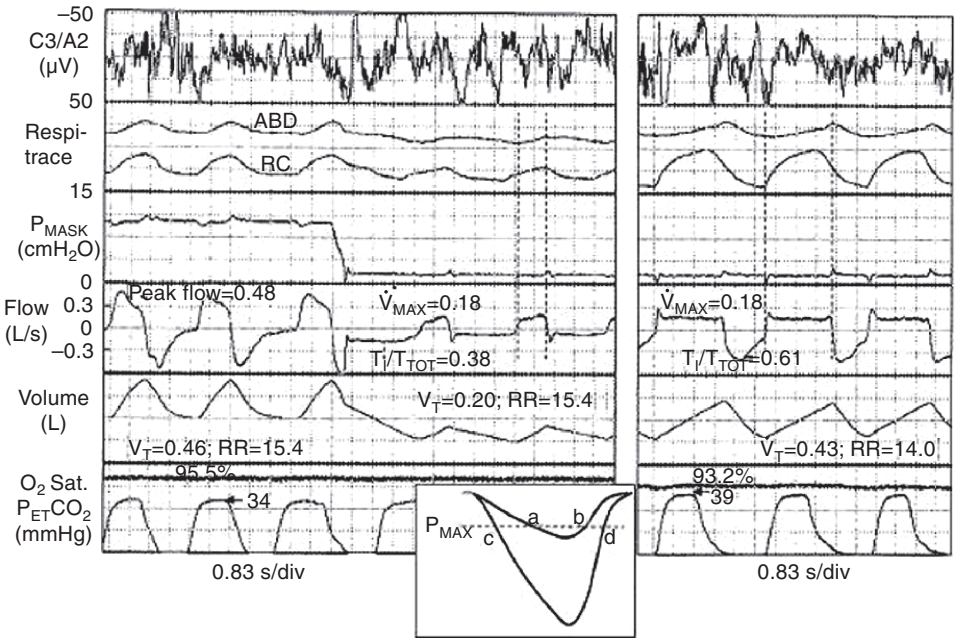

Figure 19 Tracings from a patient to show how an increase in the fraction of time spent with inspiratory flow can make it possible to tolerate maximum flows that are well below peak flow in the unobstructed state. C3/A2, central electroencephalogram showing a continuous sleep pattern; ABD, abdomen; RC, ribcage; PMASK, mask pressure; PF; peak flow; TI/TTOT, fraction of time spent with inspiratory flow; $\dot{V}_{MAX}$; maximum flow; RR, respiratory rate. (Left panel) Upon dial-down of CPAP, the patient immediately developed an obstructive hypopnea where flow was less than 40% peak flow on CPAP and tidal volume (VT) was only 43% of VT requirement. With time (right panel, 5 min later), and despite no change in $\dot{V}_{MAX}$, VT and ventilation returned to near baseline as a result of marked increase in the duration of inspiratory flow (note interval between vertical lines). There were only modest changes in end-tidal PCO_2 ($PETCO_2$) and O_2 saturation, making a steady state possible. Inset: diagram showing how an increase in the amplitude of inspiratory efforts (more negative intrathoracic pressure) can increase T_I/T_{TOT} and the time during which flow is maximum even in the absence of any prolongation in neural inspiratory time. P_{MAX}, intrathoracic pressure at which $\dot{V}_{MAX}$ is reached. The faster rate of reduction in intrathoracic pressure results in an earlier flow crossing from expiration to inspiration and $\dot{V}_{MAX}$ is reached sooner (point c vs. point a). Likewise, intrathoracic pressure remains below P_{MAX} for much of the declining phase of inspiratory effort (rising intrathoracic pressure), resulting in a delay in onset of expiratory flow and continued presence of $\dot{V}_{MAX}$ well beyond the point at which flow would have started to decline at the lower effort (point d vs. point b). Adapted, with permission, from reference 297.

effective this can be. While the patient was on CPAP (Fig. 19, left), peak flow was 0.48 L/s and $\dot{V}_E$ was 7.2 L/min. On dial down of CPAP, flow became limited and $\dot{V}_{MAX}$ was 0.18 L/s, or 37% of peak unloaded flow. V_T decreased from 0.46 to 0.20 liter, or 43% of eupneic V_T. Because respiratory rate did not change, the immediate decrease in $\dot{V}_E$ was also to 43% of the eupneic value. T_I/T_{TOT} increased gradually from 0.38 immediately after dial down (similar to the value on CPAP) to 0.61 a few minutes later (Fig. 19, right), while $\dot{V}_{MAX}$ remained the same (37% of peak unloaded flow). As a result, $\dot{V}_E$ increased from an initial 3.1 L/min at the onset of hypopnea to 6.0 L/min later on, reaching 85% of baseline $\dot{V}_E$ on CPAP. This was associated with only a 5-mmHg increase in end-tidal PCO_2 ($P_{ET}CO_2$) and a 2% reduction in O_2 saturation. These values are consistent with a new steady state. The change in chemical drive was clearly tolerated by this patient, as evidenced by continued sleep (i.e. no arousals). Thus, in this case a $\dot{V}_{MAX}$ of only 37% of peak unloaded flow was sustainable without arousal.

The importance of this mechanism lies in the fact that under appropriate conditions it can restore $\dot{V}_E$ to a sustainable level (i.e. without arousals) in the absence of any response from the pharyngeal dilators. As will be seen later, in many patients the dilators do not respond to flow limitation until chemical drive has increased to a level that causes arousal. The effectiveness of the T_I/T_{TOT} mechanism in restoring $\dot{V}_E$ to a sustainable level depends on many variables:

1. How much can T_I/T_{TOT} increase during the hypopnea: the increase in T_I/T_{TOT} during sustained loading is the result of two mechanisms (297). First, neural inspiratory time (T_I) increases and neural expiratory time (T_E) decreases as the load is sustained (174, 243, 267, 284, 297). These neural changes are linked to the increase in inspiratory effort (174, 243, 267, 284, 297). The response of neural T_I/T_{TOT} to increasing effort varies considerably among patients (213, 243), and there is evidence in mice that the duty cycle response to hypercapnia is, in part, genetically determined (213). Second, with increased effort, the inspiratory interval during which flow is maximal ($\dot{V}_{MAX}$) would increase even if neural T_I did not. This is because when inspiratory effort increases, the fraction of neural T_I during which intrathoracic pressure is more negative than the pressure required to generate $\dot{V}_{MAX}$ (i.e. P_{MAX}) is higher (Fig. 19, inset). The impact of this mechanism depends on the shapes of the rising and declining phases of the effort, and both of these vary considerably among subjects (303). Furthermore, since both neural and mechanical mechanisms of increasing T_I/T_{TOT} are related to the increase in effort, the maximum increase in T_I/T_{TOT} is also influenced by how much increase in effort can be reached before arousal occurs (i.e. arousal threshold (22, 77, 114). This also varies considerably among subjects (23, 25, 96, 226, 267, 284, 300, 308).
2. What is Maximum Inspiratory Flow: clearly, if $\dot{V}_{MAX}$ is zero ($P_{CRIT} \geq 0$), any increase in T_I/T_{TOT} would be inconsequential unless P_{CRIT} is reduced to less than 0 through recruitment of pharyngeal dilators. For P_{CRIT} less than 0, the effectiveness of a given increase in T_I/T_{TOT} in increasing $\dot{V}_E$ is a function of $\dot{V}_{MAX}$. For example, an increase in T_I/T_{TOT} from 0.4 to 0.6 when $\dot{V}_{MAX}$ is 0.1 L/s would increase $\dot{V}_E$ from 2.4 to 3.6 L/min, a difference of only 1.2 L/min. The same increase in T_I/T_{TOT} would increase $\dot{V}_E$ by 2.4 L/min^{-1} if $\dot{V}_{MAX}$ were 0.2 L/s. Thus, the milder the flow limitation, the more effective is the increase in T_I/T_{TOT}.
3. Unloaded ventilatory demand: the amount of ventilation required to maintain normal blood gas tensions varies greatly among subjects, reflecting differences in metabolic rate (e.g. as affected by body weight and muscle tone), dead space ratio, and the CO_2 set point. V_E during sleep on optimal CPAP reflects unloaded ventilatory demand and ranges from 3.8 to 9.3 L/min among sleeping subjects studied in the sleep laboratory (292, 300). The ventilation level that can be sustained without arousal during a hypopnea is not related to the absolute $\dot{V}_E$ during the hypopnea, per se, but to how much $\dot{V}_E$ during an hypopnea is as a fraction of unloaded $\dot{V}_E$ (292). This is because a give fractional reduction in $\dot{V}_E$ will produce the same changes in blood gas tensions regardless of the absolute value of $\dot{V}_E$ during the hypopnea, and it is the changes in blood gas tensions that directly or indirectly result in arousal. For example, whereas a hypopnea $\dot{V}_E$ of 4 $L.min^{-1}$ may be tolerated if unloaded $\dot{V}_E$ is 4.5 L/min (10% reduction, associated with a 4 to 5 mmHg increase in P_aCO_2), the same $\dot{V}_E$ would not be tolerated if unloaded $\dot{V}_E$ is 6 L/min (33% reduction, associated with 12 to 17 mmHg increase in P_aCO_2). It has been estimated that the sustainable $\dot{V}_E$ ranges from 80% to 95% of unloaded $\dot{V}_E$ (292). Given the wide range of unloaded ventilatory demand among sleeping OSA patients [3.8-9.3 L/min, (292)] sustainable hypopnea $\dot{V}_E$ may range from 3.0 to 8.8 L/min.

It follows that whether the increase in T_I/T_{TOT} in the course of obstructive events succeeds in restoring $\dot{V}_E$ to a sustainable level, with stable sleep and breathing, depends on many variables that include passive pharyngeal mechanics, concurrent response of pharyngeal dilators to the obstruction, metabolic rate, dead space ratio, arousal threshold, shape of the inspiratory effort waveform and, possibly, genetic factors. Many of these variables are independent of passive pharyngeal mechanics. Thus, for the same passive pharyngeal mechanics a patient with a good T_I/T_{TOT} response to increasing effort and an above average arousal threshold and/or below average metabolic demands may be stable whereas another patient with the same pharyngeal mechanics but in whom other factors are less favorable may not be able to achieve stability. Similarly, since some of these factors can change

from time to time during the same night (e.g. arousal threshold (20), metabolic demands (muscle tone), pharyngeal mechanics [e.g. supine vs. lateral (177, 292)], the patient may alternate between stable breathing and OSA as these factors change. Thus, the variable effectiveness of the T_I/T_{TOT} mechanism likely contributes importantly to the variable relation between pharyngeal mechanics and the AHI (Figs. 16 and 17).

Increased Activity of Pharyngeal Dilators

State effects on dilator activity in OSA patients

1. Muscle activation during wakefulness: the literature outlined above would suggest that most patients with sleep apnea have an anatomically small pharyngeal airway. It has been argued that this anatomic deficiency will lead to augmented muscle activity during wakefulness to maintain adequate pharyngeal patency. There is a reasonable literature that supports this concept.

   Suratt et al. (247) originally proposed that OSA patients might have greater muscle activation than healthy controls when they observed inspiratory phasic activation of the GG muscle during sleep more frequently in the apnea patients than in controls. However, his data also suggest that there was greater phasic activity awake as well. Subsequently Mezzanotte et al., using a somewhat more quantitative approach, demonstrated that OSA patients, during wakefulness, have greater genioglossal activation (quantified as a percentage of maximal muscle activity) than normal controls (Fig. 20) (156). This increased muscle activity during wakefulness in OSA patients has been confirmed in other subsequent studies (71). This augmented muscle activity could be substantially reduced in the apnea patients with continuous CPAP, but falls minimally in the normal controls (156). However, the apnea patients continued to have greater muscle activity even with CPAP in place. To our knowledge, the TP is the only other muscle whose activity has been quantitatively compared in humans between apnea patients and normal controls during wakefulness and was found to have greater activity in OSA patients than controls (157).

   Similar observations to those described earlier for the GG have been made in the sternohyoid muscle of the English bulldog, an animal model of OSA (89). This presumed upper airway dilator muscle demonstrated greater activation and more inspiratory phasic activity during wakefulness in the bulldogs than a group of beagles without sleep apnea.

   What is driving the increased muscle activity in the OSA patient has not been completely delineated. However, at least one study suggests that this may be multifactorial. Fogel et al. found two primary contributors. First, in studies of the GG muscle, they observed a similar slope between GG EMG and epiglottic pressure in apnea patients and controls (69). However, the apnea patient generated greater airway negative pressure on inspiration. Thus, the inspiratory activation of the EMG was greater in the apnea patients. Second, they reported greater tonic (expiratory) activation of the GG in the apnea patients as well (69). What drives tonic GG EMG has never been carefully studied in either animals or man. Thus, the source of this augmented tonic EMG in the apnea patient remains unclear.

2. Effect of sleep on muscle activation/control: although a number of studies have reported data on upper airway muscle activity (generally for the GG) in OSA patients across the apnea cycle, the cycling hpoxia and hypercapnia in addition to changing sleep state makes it difficult to delineate the isolated effect of sleep on muscle activity. However, several studies have examined muscle activity during the discrete transition from stable wakefulness to sleep in apnea patients and compared them to normal controls. In general, the genioglossal EMG falls quickly over the first two to three breaths following an alpha-theta transition in the apnea patient (157). This decrement is greater in the apnea patient than both middle aged and older controls groups (71). However, the genioglossal EMG remains higher in the apnea patients at sleep onset than either control group despite this decrement. After two to three breaths muscle activity is recruited and begins to rise almost certainly in response to the increased airflow resistance observed at this time point in the apnea patients (71).

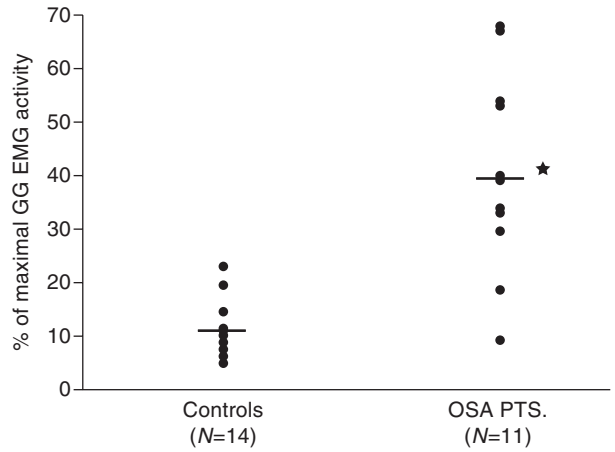

Figure 20 Peak phasic genioglossal electromyogram (EMG). Cumulative data from all subjects and patients demonstrating that in the basal state, the genioglossus functions at a higher percentage of maximum in OSA patients than controls. $^*P < 0.05$ versus controls. Adapted, with permission, from reference 156.

The TP also demonstrates a sharp decrement in activity at sleep onset in OSA patients, but this was similar to what was observed in controls (71). However, in the OSA patients, after two to three breaths, there was a recruitment of TP activity as airflow resistance rose, while muscle activity continued to decline in the control groups (71).

As stated earlier, CPAP led to a large decline in muscle activity in OSA patients and a much smaller decrement in the nonapneic controls (71, 156). During sleep onset, with CPAP in place, there was still a greater decline in GG EMG in the patients than in the controls. However, there was not an increase in airflow resistance in either group following sleep onset. Thus, GG EMG continued to decline in all groups without the recruitment seen off CPAP in the OSA group (71).

Thus, one would have to conclude that sleep onset is associated with a decrement in both genioglossal and TP activity in both apnea patients and controls. However, the decrement in GG EMG is greater in the apnea patients both on and off CPAP. Thus, one could argue that it likely represents both a loss of negative pressure-driven muscle activity and as a result of the pure loss of the wakefulness drive to the muscle. Following several breaths, as upper airway resistance rises in the OSA patients, muscle activity in both the GG and TP is clearly recruited. With CPAP in place, such that resistance cannot rise, no such recruitment occurs and muscle activity continues its decline in all groups. This clearly indicates that both the GG and TP can respond to rising airway negative pressure and chemical stimuli (hypoxia and hypercapnia) during NREM sleep.

Surprisingly, there is little information on genioglossal or other upper airway dilator muscle activity during REM sleep in patients with OSA without CPAP in place. As pure REM sleep effects would likely be difficult to discern off CPAP due to the cycling hypoxia and hypercapnia, virtually all such protocols studied patients with CPAP in place. Schwartz et al. (220) reported in a small group of OSA patients both phasic and tonic GG EMG to be substantially lower during REM than NREM sleep while on CPAP at the holding pressure (pressure required to prevent flow limitation). Similarly, in children, Katz et al. reported decreased tonic and phasic genioglosssal EMG during REM sleep compared to wake and NREM values in OSA patients on CPAP (109). They also reported a lower REM GG EMG during obstructive events off CPAP compared to any other state (wake, NREM or even REM during stable breathing) (109). Finally Eckert et al. (60) observed progressive decrements in GG EMG from wakefulness to NREM to REM sleep in OSA patients on CPAP. They also reported that the muscle activity was lowest in phasic as compared to tonic REM sleep. Thus, these studies consistently indicate a further reduction in GG EMG from NREM to REM sleep while airway pressure was positive on CPAP.

Upper airway opening at the end of obstructive events is often associated with a disproportionate increase in GG activity (202). Cortical arousals are also usually seen in the vicinity of airway opening. This association has led to the enduring notion that the disproportionate increase in GG activity is due to a state change (arousal) which introduces additional excitatory stimuli and that, by extension, a state change is required to open the airway. Although there is no doubt that arousal is responsible for upper airway opening in many cases, there is accumulating evidence that reflex (non-arousal) mechanisms are capable of opening the airway and that the occurrence of arousal in most cases is unnecessary and counterproductive. The role of arousals in the pathogenesis of OSA will be discussed in detail below.

Response of pharyngeal dilators to upper airway obstruction

A number of investigators have simply quantified the activity of upper airway dilators muscles across the apnea cycle during spontaneous OSA (42). In general, the upper airway muscles studied (GG, TP, and palatoglossus) are least active at the start of apnea and maximally active on the first breath at the end of the respiratory pause. Thus, loss of activity in these muscles is clearly important in airway closure in sleep apnea. Interpretation of these changes in terms of mechanisms is difficult in view of the usual occurrence of arousal at some point during the cycle and lack of information on the status of nonarousal stimuli (chemical drive and negative pharyngeal pressure) at the different points of measurement. However, since dilator activity is often seen to increase progressively before cortical arousal, it is reasonable to conclude that pharyngeal dilators in OSA patients can respond to increases in chemical drive with the associated reduction in pharyngeal pressure.

A number of recent studies have characterized the response of the GG to changes in chemical drive with and without airway obstruction, in the absence of cortical arousal, in OSA patients (136). Unlike the case with spontaneous recurrent events, where sleep is light and arousal threshold is low, the protocol used in these studies (136) involved placing patients on CPAP and inducing obstructions by lowering CPAP (dial-down) when sleep is deep. Arousal threshold was further increased by administration of a therapeutic dose of zopiclone. Figure 21 is a representative example of the response to a severe hypopnea induced by dialing down CPAP while the patient breathed room air. There was no evidence of arousal throughout the intervention. There was a delay of several seconds before there was any GG response. Both phasic and tonic activities increased gradually thereafter with no change in flow rate. The airway opened at the dashed line. Both phasic and tonic activities continued to increase for one or two breaths despite the open airway. Activity then subsided but some increase in activity persisted well beyond upper airway opening. The mechanism of these changes could reasonably be explained by the changes in chemical drive with the associated changes in pharyngeal pressure. However, other observations indicated that the mechanisms are more complex (see below).

Another advantage of this dial-down approach is that chemical drive could be increased to different quantifiable levels before the dial-down (136). This permitted the evaluation of GG responses to different levels of chemical drive with and without negative pharyngeal pressure (after vs. before the dial-down). Figure 22 shows an example (from reference 136). When a dial-down was performed while the patient was breathing room air (panel A), a severe hypopnea resulted during the first dial down breath. There was no associated

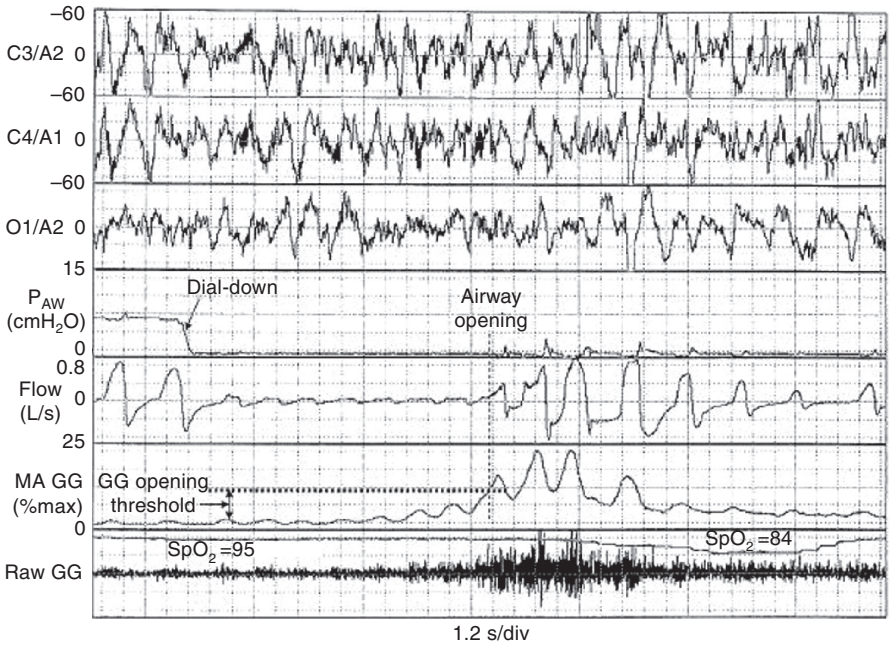

Figure 21 Response of genioglossus activity to an induced severe hypopnea in the absence of cortical arousal. C3/A2, C4/A1, and O2/A1 are three electroencephalography leads; P_{AW}, airway pressure; MA GG, moving average of genioglossus activity; GG opening threshold, increase in GG activity level at which the airway opened. Note the progressive increase in both tonic and phasic GG activities and that both activities remained higher than at the beginning of the obstruction well beyond upper airway opening. The second obstructive event is milder than the first.

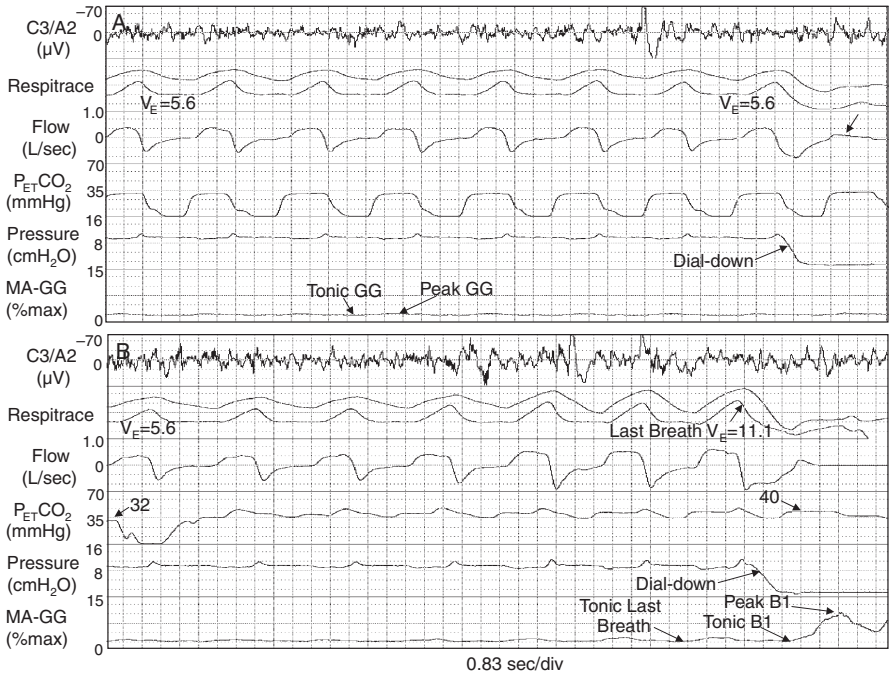

Figure 22 Tracings illustrating an example of the response to increasing chemical drive on continuous positive airway pressure (CPAP) and immediately following induced obstruction. C3/A2: electroencephalogram. $P_{ET}CO_2$: airway PCO2. MA-GG: moving average of genioglossus activity, expressed as percent of maximum activity. (A) Patient breathing room air. CPAP was reduced to 1.0 cmH_2O (dial-down) inducing a severe hypopnea (arrow in flow tracing). Note that there was no increase in genioglossus activity during the obstructed breath. (B) In the same patient, inspired CO_2 was increased for 30 s prior to dial-down. Note that genioglossus activity increased little on CPAP despite doubling of ventilation (VE). However, there was a large increase in genioglossus activity following dial-down. Adapted, with permission, from reference 136.

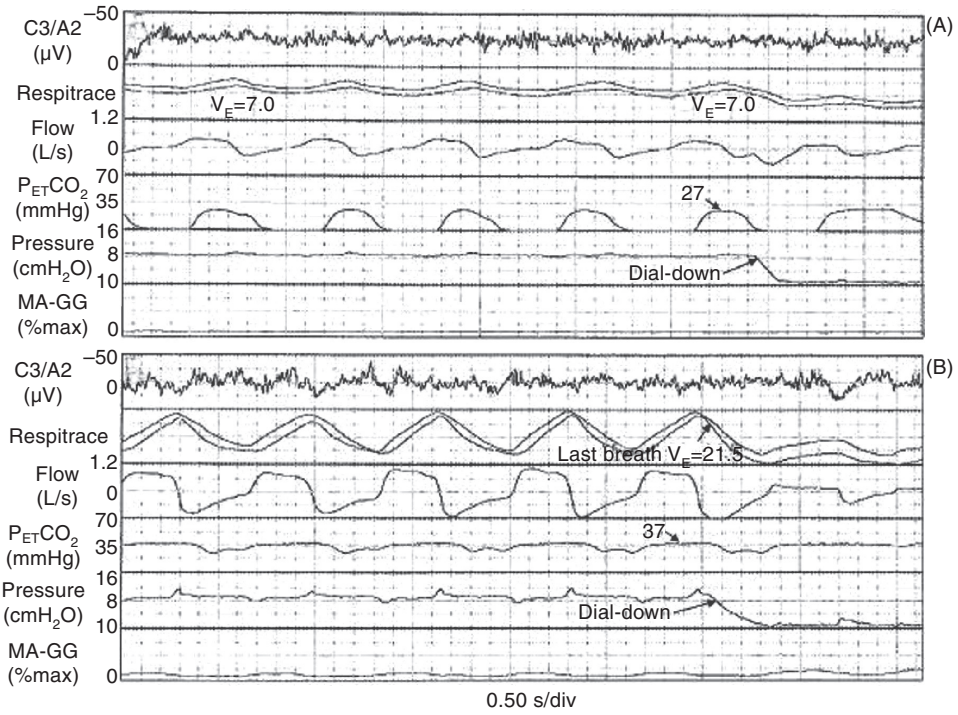

Figure 23 Tracing from a patient showing failure of genioglossus activity to increase appreciably during the first obstructed breath despite a 3-fold increase in ventilation prior to dial-down (compare last breath in panels A and B). This patient had only mild hypopnea during dial-down from air breathing (A), indicating mild abnormalities in pharyngeal mechanics (P_{CRIT} was −10 cmH_2O). His apnea-hypopnea index was 68 h^{-1}. Adapted, with permission, from reference 136.

increase in GG activity. This observation is in agreement with previous findings (127, 244) and indicates that the negative pressure developed during obstructed breaths is insufficient to engage the negative pressure reflex when chemical drive is eupneic (i.e. unstimulated). However, when chemical drive was increased prior to the dial down ($\dot{V}_E = 11.1$ vs. the eupneic level of 5.6 L/min, panel B), there was a brisk increase in phasic activity during the first obstructed breath. Thus, the obstructed pharyngeal pressure associated with twice the eupneic drive was sufficient in this case to elicit a response. Intermediate levels of ventilatory stimulation were also insufficient to elicit a response in this patient. In other patients, this threshold is much higher (e.g. Fig. 23 from reference 136). With further increases in chemical drive above the threshold level GG activity increases progressively but the rate of increase also varies greatly among patients (see Section "Effective Recruitment Threshold (T_{ER})").

In the same study (136), it was found that GG activity increased little when chemical drive was increased while patients were on CPAP (e.g. Figs. 22B and 23B). Thus, in 17 of 20 patients the increase was less than 1% GG_{MAX} over a wide range of ventilatory stimulation (up to 4-fold eupneic $\dot{V}_E$). This finding is different from the results of another study in normal subjects (134) where CO_2 stimulation during CPAP administration was associated with much larger increases in GG activity. It is not clear whether the different results reflect differences between normal subjects (134) and OSA patients (136); there were several technical differences that could have accounted for the different responses as well (136). Regardless, it appears that important recruitment of GG in OSA patients requires the presence of negative pharyngeal pressure. Whether the recruitment at the higher chemical drive is strictly related to the more negative pharyngeal pressure or the increase in chemical drive must be present simultaneously for the reflex to be elicited is not known.

Whereas the progressive increase in phasic activity with sustained obstruction (Fig. 21) may be attributed to the progressive increase in respiratory drive and the more negative pharyngeal pressure, the progressive increase in tonic activity (Fig. 21) cannot be explained by the same mechanism. Pharyngeal pressure during expiration is positive and not negative. Furthermore, tonic activity does not respond appreciably to changes in chemical drive in the absence of inspiratory obstruction. In the study by Loewen et al. (136) tonic activity increased less than 0.3% GG_{MAX} at 3-fold eupneic $\dot{V}_E$ when chemical drive was increased in the absence of prior obstructed inspirations. These observations suggested that recruitment of tonic activity is related to a memory phenomenon. One further advantage of the brief dial down approach is that by raising the CPAP to its predial-down level after some GG response has developed, but before arousal, it is possible to compare activity at two equal ventilation levels (i.e. same chemical drive) before and after the obstructive event (299). A higher activity at iso-ventilation on CPAP after

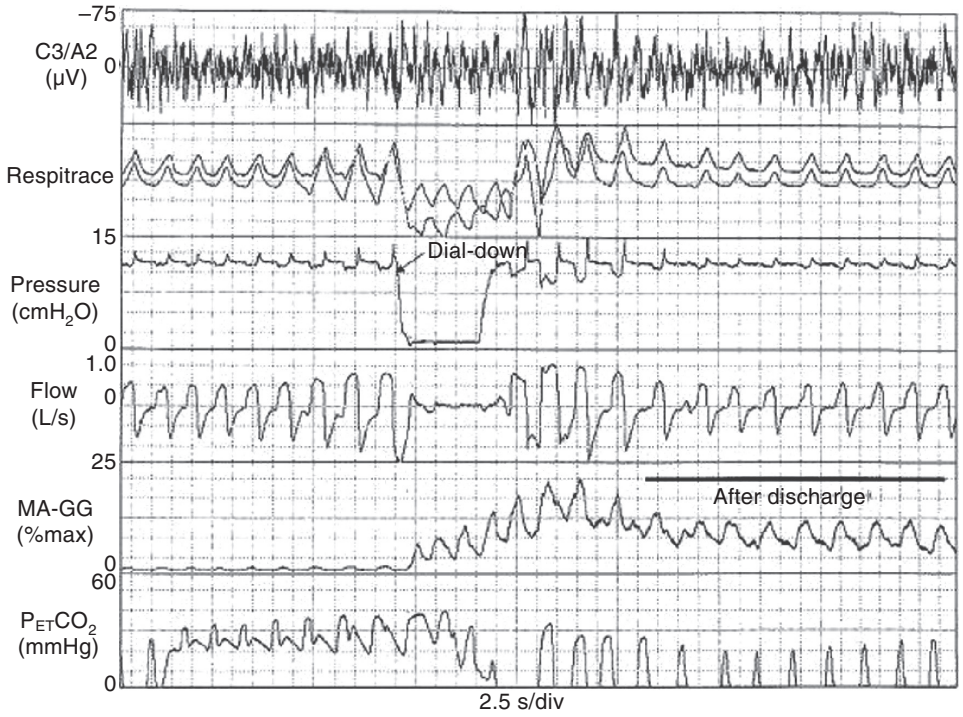

Figure 24 Tracings illustrating strong short-term potentiation (STP) in a patient with obstructive apnea. C3/A2, electroencephalogram; MA GG, moving average of genioglossus activity. An apnea was induced by lowering CPAP pressure at arrow (dial-down). Ventilation was stimulated prior to the dial-down to advance GG recruitment. The obstruction was relieved by reinstituting optimum CPAP prior to arousal. Ventilation returned within a few breaths to or below the levels observed prior to the dial-down (period covered by the solid horizontal bar). Note the increase in tonic activity during the obstruction. Also note that both phasic and tonic GG activities remained higher than activities prior to dial-down despite comparable or lower ventilation. Unpublished observations.

the brief obstructive episode would indicate the operation of another mechanism that is not directly related to instantaneous chemical drive and its immediate consequences (e.g. pharyngeal pressure). Figure 24 is an example (from reference 299). Note that both phasic and tonic GG activities are higher on CPAP after the brief dial down than before even though ventilation is comparable (heavy bar). Both declined gradually toward predial-down activity (299) but the increase in tonic activity outlasted the increase in phasic activity and was even observed when a central apnea (not shown) followed the ventilatory overshoot, when there were no inspiratory efforts or phasic GG activity. These observations are consistent with the operation of short-term potentiation (STP), a widespread neurophysiological response to sustained stimuli that has been well documented also in diaphragmatic responses to chemical stimuli (65). The magnitude of increase in tonic activity during the obstruction and the magnitude of the post event increase in tonic activity (after-discharge) varied greatly among subjects [(299), e.g. compare Figures 24 and 25].

In addition to after discharge, there is a substantial literature assessing more long-term memory in the respiratory control system, with long-term facilitation (LTF) being a prominent component of this memory. LTF is an increase in ventilation lasting up to several hours following exposure to intermittent hypoxia of relatively short duration (173). Thus, hyperventilation continues without obvious chemical stimulus. This increased ventilation has been reported for years in animals (both anesthetized and awake) and more recently in humans (9, 10, 84, 192), although not all studies found LTF in man (151). More sustained intermittent hypoxia has been observed to augment this response (152). In humans, the early studies suggested that intermittent hypoxia during sleep in snorers led to an increase in minute ventilation during sleep and it was hypothesized that this was secondary to increased pharyngeal dilator muscle activation, thereby reducing airflow resistance (9, 10). Later work suggests this augmented ventilation can occur in non-snorers as well (192). Subsequent human studies indicated that LTF could be induced in awake humans if the arterial PCO_2 was raised 5 mmHg over the eupneic level (84). Finally, and most important to this discussion, animal and subsequent human studies indicate that intermittent hypoxia leads to increased upper airway muscle activation (particularly genioglossal) in a pattern similar to the increase in ventilation described previously (50, 208). Thus, LTF could decrease apnea severity over time if there is a sustained increase in upper airway dilator muscle activity. However, there is no direct evidence that LTF is active in OSA patients or that it reduces the AHI in these patients.

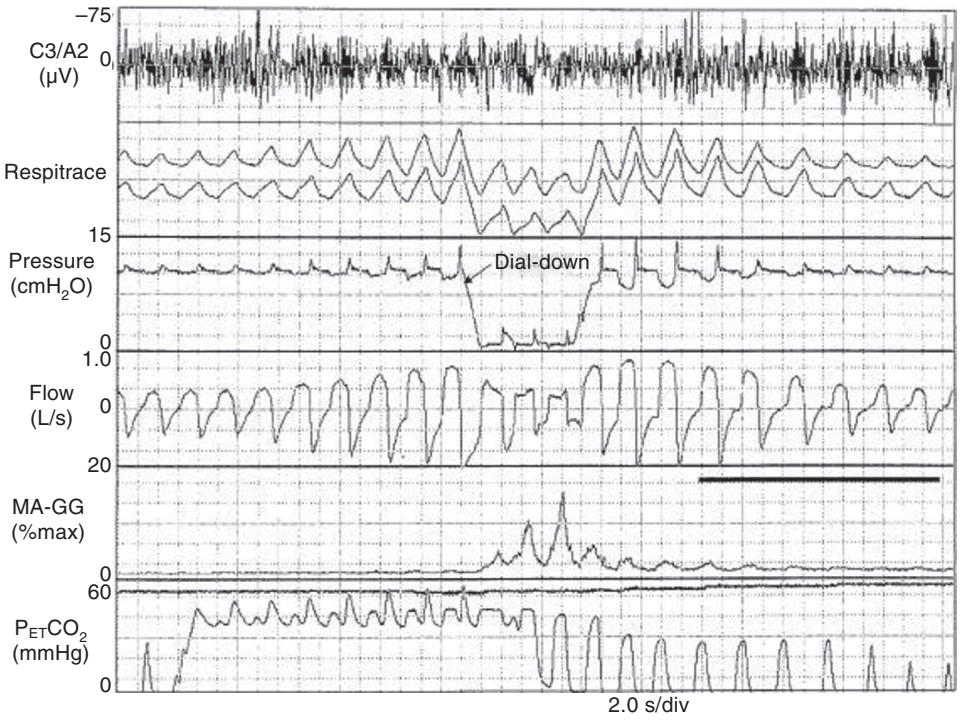

Figure 25 Tracings illustrating lack of short-term potentiation (STP) in a patient with obstructive apnea. C3/A2, electroencephalogram; MA GG, moving average of genioglossus activity. An obstructive hypopnea was induced by lowering CPAP pressure at arrow (dial-down). Ventilation was stimulated prior to the dial-down to advance GG recruitment. The obstruction was relieved by reinstituting optimum CPAP prior to arousal. Ventilation returned within a few breaths to or below the levels observed prior to the dial-down (period covered by the solid horizontal bar). Note minimal increase in tonic activity during the obstruction and lack of sustained increase in either tonic or phasic GG activity post obstruction at comparable levels of ventilation. Unpublished observations.

Mention has been made earlier of the presence of periods of stable breathing under conditions where OSA is otherwise present (292). Jordan et al. (107) found that GG activity is elevated during these stable periods. Because chemical drive during stable breathing was not known, it could not be ascertained whether the higher activity was related to a higher chemical drive (107). The recent findings about the existence of STP (299) makes it likely that STP plays a role in generating these stable periods, with STP in such cases being maintained by some flow limitation and above normal negative pharyngeal pressure. In fact, since tonic activity does not increase at higher chemical drives unless pharyngeal pressure is negative on inspiration (136) and the increase under these conditions is due to STP (299), any increase in tonic activity during stable breathing is likely mediated by STP or LTF.

Jordan et al. also recently reported that following a sustained dial-down of CPAP, GG activity during the second hypopnea was higher than it was in the first hypopnea (i.e. similar to Fig. 21), and that whether or not a cortical arousal was observed following the first hypopnea did not affect the GG activity in the second hypopnea (105). The authors attributed the higher GG activity in the second hypopnea to a long lasting postarousal effect; the continued presence of this higher activity in the absence of a preceding cortical arousal was attributed to arousals occurring in the brain stem that are not transmitted to the cortex. With the demonstration of STP in the control of upper airway dilators, STP is a more likely explanation for the higher activity in subsequent hypopneas.

Figure 26 summarizes the sequence of events that follow the onset of an obstructive event. In OSA patients, the dilator activity available during sleep at eupneic chemical drive is not enough to overcome the collapsing forces acting on the passive pharynx. Chemical drive must rise above eupneic levels in order for the airway to open and to stay open. Dilator activity increases as chemical drive increases during the obstructive event, but in many patients the response does not begin until chemical drive has increased to a threshold amount above eupnea (recruitment threshold). Thereafter, unless interrupted by an arousal, dilator activity increases in response to further increases in chemical drive and, possibly, as a consequence of STP. Activity continues to increase until it can overcome the collapsing forces acting on the pharynx (dilator opening threshold). At this point, the airway opens. Dilator activity increases for one or two breaths beyond opening. Thereafter, activity decreases as chemical drive decreases but it remains higher at the same chemical drive on account of

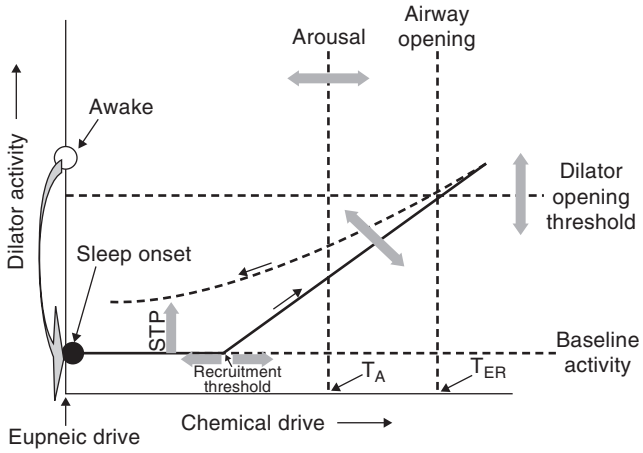

Figure 26 Sequence of events following the onset of an obstructive event. At eupneic drive, dilator activity during sleep is less than the level required to keep the airway open. A hypopnea or apnea develops. Chemical drive increases. At a certain chemical drive (recruitment threshold), which varies greatly from patient to patient, the dilators begin responding to further increases in drive. The rate at which activity increases beyond the recruitment threshold is also highly variable. Activity increases until the level required to open the airway (dilator opening threshold) is reached. This threshold varies from 1% to 37% of GG_{MAX} among patients. Activity increases for one or two breaths beyond the point of opening and then begins declining as chemical drive decreases. In the declining phase activity is higher than at the same drive in the rising phase as a result of short-term potentiation (STP). Both the dilator opening threshold and the gain of STP are highly variable. The chemical drive at which dilator activity reaches Dilator Opening Threshold is referred to as effective recruitment threshold (T_{ER}). This sequence can be interrupted if the arousal threshold (TA) is less than T_{ER}.

STP (dotted line). The increase in chemical drive above eupnea that is required to increase dilator activity to a level that can open the airway has been termed the "effective recruitment threshold" or T_{ER} (297, 300). T_{ER} has been found to vary from just above eupneic drive to greater than 3-fold eupneic levels (i.e. comparable to more than 3-fold increase in $\dot{V}_E$ in the absence of obstruction) (136, 297, 298). All factors that influence the response (dilator recruitment threshold, rate of rise in dilator activity, dilator opening threshold, arousal threshold, and STP) are highly variable among patients (136, 298-300).

Mechanisms of Ventilatory Instability in OSA Patients

It is clear from the aforementioned discussion that pharyngeal dilators can respond to the increase in chemical drive and the associated increased negativity of pharyngeal pressure in the absence of arousal. Thus, given the opportunity through progressive increase in chemical drive, the dilators should be able to open the airway without arousal in most patients (296, 298). Indeed, in nearly half of the spontaneous obstructive events upper airway opening occurs without or before the onset of cortical arousal. The occurrence of stable breathing and sleep in many patients in whom pharyngeal mechanics are grossly abnormal [e.g. $P_{CRIT} > 0$, Figure 18 and references (292) and (106)] is further evidence that nonarousal mechanisms are capable of compensating for the abnormal pharyngeal mechanics without arousal.

The only known nonarousal mechanisms that can activate pharyngeal dilators during sleep are (a) an increase in chemical drive and (b) a more negative pharyngeal pressure. In the setting of upper airway obstruction, pharyngeal pressure can become more negative only if pressure output of the pump muscles (e.g., diaphragm) increases. Since during sleep pressure output of these pump muscles can increase only if chemical drive increases (295), an increase in chemical drive above eupnea is required to activate the dilators enough to open the airway without arousal (296, 297). As a corollary, chemical drive must remain elevated above a certain level in order for the upper airway to remain open with continuous sleep. If drive increases above the required level but decreases again below it when the airway opens, recurrent obstructions would result (296, 297). For chemical drive to remain elevated beyond an initial obstructive event, flow cannot increase much above eupneic demand when the airway opens. The occurrence of a significant ventilatory overshoot would wash away the chemical stimulus required to keep the airway open, setting the stage for another obstruction. Yet OSA patients routinely develop an overshoot at the end of obstructive events. A recent study found that the increase in flow at airway opening was 2.56 ± 1.69 times the amount required to satisfy eupneic demand (296). Thus, the reason why OSA patients develop recurrent obstructions is that their ventilation overshoots the target upon airway opening (296, 297), thereby reducing the chemical drive below the level required to maintain adequate dilator activity.

From the aforementioned discussion, it follows that OSA is an example of chemical control system instability. The main difference from recurrent central apneas (e.g. Cheyne-Stokes breathing) is that the flow is limited and not responsive to chemical drive (i.e. obstructive apnea threshold) chemical drive below which is higher than the central apnea threshold. This is because, unlike the diaphragm, the UA dilators, whose activity determines the level of ventilation in such patients, require a higher level of drive to begin responding to PCO_2 and Po_2. Thus, factors that promote central apneas also promote obstructive apneas. However, as discussed later in detail, the presence of upper airway instability introduces additional factors that affect plant gain and controller gain (112, 137, 293). These include (a) the duration of the obstructive events, which greatly affects the magnitude of blood gas tension changes before there is a ventilatory response (plant gain) and essentially acts as a long circulation delay, (b) the extent to which the airway opens at the end of the obstructive events, which affects the ventilatory response to the blood gas tension changes (controller gain), and (c) whether arousal occurs before the required increase in chemical drive is reached. To understand these differences, it is helpful to briefly review the factors that generally contribute to instability.

Chemical Control Loop Gain (General)

When a transient disturbance in ventilation occurs (e.g. a hypopnea or an apnea) blood gas tensions change. These changes reach the chemoreceptors and elicit responses that tend to correct the disturbance. For example, a hypopnea results in an increase in P_aCO_2 and a decrease in P_aO_2. These changes will result in stimulation of the respiratory muscles, via chemoreceptor feedback, which in turn will result in an increase in ventilation. Loop gain (LG) is the ratio (response/initial disturbance). If the ratio is greater than 1, the system is unstable because, in the case of a transient hypopnea, the response will result in a ventilatory overshoot that is greater than the inverse of the original hypopnea, which will result in greater but opposite changes in blood gas tensions. These would lead to a second hypopnea and the cycle repeats. The factors that determine LG are listed below and these include modifications to allow for the differences between Cheyne-Stokes breathing and recurrent OSA.

1. How much will blood gas tensions change before there is a ventilatory response? It is clear that the more severe the hypopnea and the longer it lasts, the more the blood gas tensions will deteriorate before there is a ventilatory response that reverses these changes. These maximum (worse) changes (ΔP_aCO_{2MAX}, ΔP_aO_{2MAX}) will ultimately reach the chemoreceptors. The final response will necessarily be a function of these "worse" changes. Taking the case of ΔP_aCO_{2MAX} (similar considerations apply to ΔP_aO_{2MAX}):

$$\Delta P_aCO_{2MAX} = \Delta \dot{V}_E{}^* G_P$$

where G_P is a function of ΔT and $\Delta \dot{V}_E$ is the change in minute ventilation during the hypopnea (or apnea). ΔT is the time between the onset of the hypopnea and the appearance of a first ventilatory response (in seconds). G_P is plant gain, which is the maximum change in P_aCO_2 per unit change in $\dot{V}_E$ (in mmHg/L/min). In the steady state ($\Delta T =$ infinity) it is determined by metabolic rate and the dead space ratio, as dictated by the metabolic hyperbola. In the dynamic state, for example, soon after a hypopnea onset, it is also determined by multiple other factors including lung volume and cardiac output (47, 112, 113, 137, 293, 301). These factors determine the rate at which blood gas tensions will change toward the steady state values. Most relevant to this analysis is the fact that dynamic G_P, and hence ΔP_aCO_{2MAX}, increases as a function of ΔT (i.e. as a function of the duration of the obstructive event). With the exception of ΔT, factors that determine ΔP_aCO_{2MAX} are the same whether the hypopnea or apnea is central or obstructive. In the usual analysis of ventilatory instability (i.e. in the absence of upper airway obstruction) ΔT is simply the lung to chemoreceptor circulatory delay, which is typically less than 10 s (300). In the presence of upper airway obstruction, the upper airway need not open as soon as chemoreceptors activity begins increasing (136). Thus, a ventilatory response will only develop when the upper airway opens at the end of the event. Event duration (and hence ΔT) is, on average, 18 s (296) and may be as long as 90 s. This difference in ΔT can greatly increase plant gain and, by extension, ΔP_aCO_{2MAX}, even when circulatory delay is normal. Accordingly, factors that increase event duration are particularly destabilizing [see Section "Effective Recruitment Threshold (T_{ER})"].

2. How much will ventilation increase in response to ΔP_aCO_{2MAX}? The ventilatory response to ΔP_aCO_{2MAX} ($\Delta \dot{V}_E$ Response) is given by (47, 112, 113, 137, 293, 301):

$$\Delta \dot{V}_E\text{Response} = \Delta P_aCO_{2MAX}{}^* G_C$$

where G_C is dynamic controller gain and is also a function of ΔT. Dynamic controller gain increases with ΔT because the longer a given change in P_aCO_2 is maintained, the more central chemoreceptors, which have longer dynamics than peripheral chemoreceptors, become activated. In the usual analysis of ventilatory instability (i.e. in the absence of airway obstruction), G_C is the dynamic ventilatory response to CO_2 (in L/min/mmHg) at $\Delta T =$ circulatory delay and it is assumed that there is a linear relation between respiratory muscle pressure generation and minute ventilation (i.e. constant impedance). There are two major differences between instability with open airway and instability with a collapsible airway in this respect. First, in the case of obstructive events, ΔT is much longer than the circulatory delay, which increases controller gain. Second, impedance is not constant. During the obstructive event, pressure output of the respiratory muscles increases with no increase in $\dot{V}_E$ and impedance is, therefore, almost infinite. When the airway opens, impedance may be normal (if the airway opens fully) or intermediate between normal and infinity (partial opening of the airway). Thus, for analysis involving instability in OSA, it is necessary to partition G_C into two components, G_{PMUS}, the increase in respiratory muscle pressure per unit increase in PCO_2 (in cmH_2O/mmHg) and impedance (in cmH_2O/L/min). The equation that governs $\Delta \dot{V}_E$ response can accordingly be rewritten:

$$\Delta \dot{V}_E\text{Response} = \Delta P_aCO_{2MAX}{}^* G_{PMUS}/I_{RS}$$

where I_{RS} is the instantaneous impedance of the respiratory system and G_{PMUS} is a function of ΔT. It will be noted that the final product of this equation is in units of L/min.

Substituting $\Delta \dot{V}E^* G_P$ for ΔP_aCO_{2MAX}

$$\Delta \dot{V}_E\text{Response} = \Delta \dot{V}_E{}^* G_P{}^* G_{PMUS}/I_{RS}$$

LG in the setting of OSA can thus be expressed by the following formula:

$$\begin{aligned} LG &= \Delta\dot{V}_E Response/\Delta\dot{V}_E \\ &= [\Delta\dot{V}_E{}^{*}G_P{}^{*}G_{PMUS}/I_{RS}]/\Delta\dot{V}_E \\ &= G_P{}^{*}G_{PMUS}/I_{RS} \quad (1) \end{aligned}$$

where G_P and G_{PMUS} are functions of event duration and I_{RS} varies between normal and infinity depending on the state of patency of the upper airway. It can be seen that LG in OSA is affected by the same factors that affect stability in the absence of upper airway instability except that G_P and G_{PMUS} are now functions of event duration and not of circulatory delay, and controller gain is variable, depending on how patent the upper airway is. Thus, if abnormal, other factors that affect plant gain (e.g. lung volume and cardiac output) and factors that affect G_{PMUS} (e.g. chemoresponsiveness, respiratory muscle strength) play the same role here as they do in central hypopnea/apnea. When LG is measured on optimal CPAP, G_P and G_{PMUS} become functions of circulatory delay (there is no upper airway obstruction to be opened before a response can be elicited) and I_{RS} is normal and constant. LG under these conditions reflects the stability of the basic chemical control in the absence of upper airway collapse. When recurrent OSA is present LG is, by definition, greater than 1. When LG on CPAP is near 1, very little destabilizing influences related to upper airway instability can raise the overall LG to greater than 1, and OSA develops. By contrast, if LG on CPAP is near zero, more severe abnormalities related to upper airway instability must be present before the system oscillates.

Reference has been made to the fact that for the airway to be open in an OSA patient, chemical drive must exceed eupneic drive by a threshold amount. Below this threshold drive (effective recruitment threshold; T_{ER}) the airway is obstructed and there is no ventilatory response to changes in chemical drive. Another very important difference, therefore, between the instabilities of central apnea and obstructive apnea is that in central apnea there is only one PCO_2 threshold below which apnea develops (central apnea threshold), and this threshold is invariably below eupneic levels of PCO_2. By contrast, in obstructive apnea there are two apnea thresholds, one for complete cessation of efforts, which is the same as the central apnea threshold, and a higher one below which there are efforts but the airway is obstructed and ventilation is unresponsive to changes in chemical drive. Because the central apnea threshold is below eupneic drive while the obstructive apnea threshold (T_{ER}) is above eupneic drive, there is a drive range between the two thresholds (Fig. 27). Should the ventilatory overshoot force PCO_2 below the central apnea threshold, central apnea will appear first as PCO_2 rises and this will be followed by a period of obstructed breaths until chemical drive is above T_{ER}. At this point the airway opens. A mixed apnea is the result (Fig. 27). Should the ventilatory overshoot reduce chemical drive into the range between central apnea threshold and T_{ER}, a pure obstructive event develops (Fig. 27). It should also be evident that if the difference between central apnea threshold and T_{ER} is small the entire range may be crossed in a few seconds as PCO_2 rises after the overshoot, particularly if the rate of rise of drive is fast (high G_P or G_{PMUS} gain). In this case, no obstructed breaths occur following the central apnea and a pure central apnea is the outcome. Thus, in the presence of upper airway mechanical instability, mixed, obstructive, or central apneas may develop depending on the magnitude of the overshoot, LG, and the difference between central apnea threshold and T_{ER}.

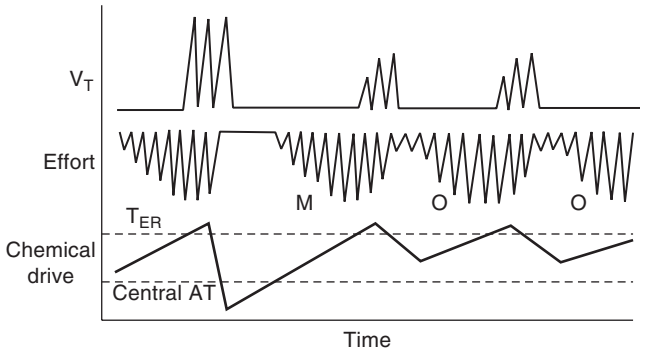

Figure 27 Schematic illustration of the events that lead to mixed or obstructive apneas. There are two chemical drive thresholds, the central apnea threshold (central AT) below which there are no respiratory efforts, and an obstructive apnea/hypopnea threshold below which there are efforts but the airway is obstructed and flow is unresponsive to chemical drive (i.e. effective recruitment threshold; T_{ER}). In the first sequence, the efforts increase, but with no ventilatory response, as chemical drive increases in the range between the two thresholds. Finally, as T_{ER} is crossed, the airway opens. A large overshoot develops that forces chemical drive below the central AT. A central apnea develops followed by a number of obstructed breaths as chemical drives cross between the two threshold (mixed apnea; M). In the second and third sequences, the ventilatory overshoot was not as pronounced and chemical drive decreases into the range between the two thresholds. An obstructive apnea/hypopnea develops (O).

In the next few sections, we will describe the contribution of different factors to the instability in OSA patients. These include the basic chemical control LG (i.e. in the absence of upper airway instability), arousals, and the effective recruitment threshold (T_{ER}).

The Basic Chemical Control Loop Gain in OSA Patients

Is basic chemical control loop gain increased in OSA patients?

A number of studies have evaluated LG, or some of its components, in OSA patients under conditions where the response measured can be directly attributed to basic chemical control LG (i.e. unaffected by variable impedance, arousals, or obstructive event duration).

Hudgel et al. (95) found that the dynamic response of $\dot{V}_E$ to a single breath increase in inspired CO_2 is higher in awake OSA patients than in normal subjects. The response

so measured reflects plant gain and controller gain when ΔT is the circulatory delay and there are normal stable mechanics. However, this study was done in awake upright subjects breathing oxygen.

The breath-by-breath increase in $\dot{V}_E$ during NREM sleep on CPAP was determined following step changes in inspired gases in 21 patients with severe OSA [AHI = 91 ± 24 h^{-1} (300)]. By use of different gas mixtures it was possible to estimate the breath-by-breath increase in chemical drive following sudden elimination of alveolar ventilation, as would occur following the onset of an apnea or a severe hypopnea. As expected from the circulation delay, there was no increase in drive ($\dot{V}_E$) until breath 3. Beyond breath 3 the rate of increase was, on average, a remarkable 8.9 ± 5.0 $L.min^{-1}$, or 134 ± 77% of eupneic $\dot{V}_E$, between breaths 3 and 5 (297,300). These values are affected by plant gain and controller gain when ΔT is the circulatory delay and mechanics are normal and stable. In the absence of comparable values in normal sleeping subjects it is difficult to determine how excessive this is. However, when these patients were reevaluated after an average 10 months of CPAP therapy, the responses had decreased to less than half the pretherapy values, thereby indicating that basic chemical control LG was markedly elevated before therapy (135). Because factors that affect plant gain were not altered by CPAP therapy [circulatory delay, BMI (and hence functional residual capacity)], the increase in LG was primarily due to a higher controller gain.

The rate of increase in intrathoracic pressure prior to arousal in the course of naturally occurring obstructive events ($\Delta P/\Delta t$) is also a good reflection of basic chemical control LG, as it is affected by plant gain and G_{PMUS} when ΔT is the circulatory delay. Respiratory impedance is infinite in this case but the response reflects LG up to the step of conversion of P_{MUS} to ventilation. $\Delta P/\Delta t$ during naturally occurring events in OSA patients ranged between 1.0 and 2.0 $cmH_2O.s^{-1}$ in different studies (23,24,25,226,284,308). This is to be compared with a rate of 0.35–0.70 $cmH_2O.s^{-1}$ in normal subjects in whom the airway was occluded during sleep (26,27,28).

Proportional assist ventilation (PAV) is a method of partial ventilatory support with which the ventilator delivers pressure in proportion to P_{MUS} (294). As a result, a given change in P_{MUS} results in a greater increase in ventilation. The net effect is a quantifiable increase in controller gain and, by extension, LG. When PAV gain is gradually increased while the patient is on CPAP a point is reached when the patient develops periodic breathing with central apneas (154, 155). At this point LG is 1.0. The native LG can be estimated from the PAV gain that had to be used to reach a LG of 1.0. The advantage of this method is that it directly evaluates overall LG. However, the procedure is difficult because of the frequent occurrence of arousals prior to development of periodic breathing. Nonetheless, several studies have used PAV to measure LG in normal subjects (154, 155, 274, 276) and in patients with sleep apnea (105,273,276,301). In normal subjects, LG is very low [usually <0.3; (154, 155, 274, 276)]. In patients with OSA, LG measured on CPAP was higher but invariably less than 1.0 (105,273,301) indicating that, without additional destabilizing factors, OSA patients would not be unstable.

In summary, there is evidence that the basic chemical control LG is elevated in patients with OSA but not elevated enough to be entirely responsible for the instability. As such, it may only be a contributing factor. The increase in basic LG appears to be primarily due to a higher controller gain although plant gain may also be elevated in obese patients (because of lower lung volume) and in those with concomitant cardiac insufficiency and long circulation delay. At least some of the increase in controller gain appears to be acquired in the course of untreated OSA.

How does the increased basic loop gain affect instability?

An increase in basic LG may contribute to instability in two ways. First, because of the obligate circulatory delay the chemoreceptors are always responding to the gas tensions that were in the pulmonary capillaries one or two breaths earlier. Thus, when the airway opens, as a result of arousal or nonarousal mechanisms, the opening is in response to gas tensions that were in the lungs a circulation delay earlier. In the interval, pulmonary gas tensions had deteriorated further and these gas tensions will ultimately reach the chemoreceptors. As a result, chemical drive continues to increase for one or two breaths beyond airway opening (Fig. 26). The rate at which chemical drive increases during the obstructive event is determined by basic LG. Thus, with a higher basic LG chemical drive would rise more postevent before it begins declining. This would increase the postevent overshoot because of a higher likelihood of arousal occurring, a greater increase in pump muscle activity postevent, and greater recruitment of dilators with a greater reduction in respiratory impedance during the overshoot. Second, with a higher basic LG chemical drive increases at a faster rate during the obstructive event. Therefore, the drive required to open the airway with or without arousal would be reached sooner (Fig. 26). Event duration would be shorter and the frequency of cycling (AHI) would increase.

A high basic LG can also affect the expression of the obstructive events. Xie et al. (290) found that for the same P_{CRIT}, patients with a higher basic LG are more likely to develop mixed/central apneas than those with a lower LG. This is likely because of the impact of LG on the magnitude of the overshoot, as described earlier and in Figure 27.

Is the increased basic loop gain clinically important?

An important question is whether the observed changes in basic LG are sufficient to alter the clinical severity of OSA. Because basic LG can be reduced by several interventions (e.g., oxygen or CO_2 inhalation, acetazolamide), the demonstration of an important contribution of this mechanism to

OSA severity may make it possible to utilize such interventions for therapy, at least in some patients. Wellman et al. (273) found a weak correlation between AHI and LG (measured on CPAP with PAV) ($r = 0.36$). Interestingly, when the relation was looked at separately in patients with mild ($P_{CRIT} < -1$ cmH_2O) or severe ($P_{CRIT} > 1$ cmH_2O) anatomic abnormalities there was no correlation between AHI and LG. On the other hand, in the group with P_{CRIT} between –1 and 1 cmH_2O, the correlation was excellent ($r = 0.88$). Thus, it appears that a high basic LG may play an important clinical role in a subset of patients with a moderate anatomical abnormality. It must be pointed out that a positive correlation between AHI and LG does not establish a cause and effect relation. However, in a subsequent study, Wellman et al. (276) evaluated the effect of reducing basic LG with oxygen breathing on the AHI in six patients with high LG (0.62 ± 0.18) and six patients with low basic loop gain (0.24 ± 0.04). They found that oxygen had no effect in patients with low LG but the AHI decreased significantly (63 ± 34 to 34 ± 30 min^{-1}) in the group with high LG. These results suggest that a high LG does in fact increase the AHI in some patients but, because the AHI was still high on oxygen (34 ± 30 min^{-1}), oxygen alone may not be sufficient for therapy in these patients.

Arousals in OSA Patients

What is an arousal?

Electrocortical arousals are extremely common in OSA. Arousal frequency may range up to 100 h^{-1} or more. The term arousal denotes a temporary state change from sleep to wakefulness. As such, frequent arousals have clinical significance in that they result in sleep fragmentation. Sleep fragmentation may impair cognitive function, even in the absence of concomitant hypoxemia (52, 68, 203).

There are major differences in opinion regarding what constitutes an arousal in the setting of OSA. The standard definition recommended by the American Academy of Sleep Medicine and the American Sleep Disorders Association (1, 2) is "an abrupt shift in EEG to a higher frequency, including alpha, theta, or beta, for at least 3 s with at least 10 s of stable sleep preceding the change." Some argue that this definition is too restrictive in that high-frequency shifts of shorter duration (1-3 s), or even a single K complex or two delta waves in succession, occurring near the end of an obstructive event should be considered as arousals (e.g. reference 257). Some even argue that EEG changes are not necessary to score arousals; an increase in heart rate or blood pressure, as reflected for example by pulse transit time, in the context of a respiratory event should suffice (57, 105, 201, 257). These are referred to as "subcortical," "brainstem," or "autonomic" arousals, collectively referred to as "subcriterion" arousals (105, 257).

The definition of what is an arousal is of considerable importance here for two reasons. First, from the clinical standpoint, using too lax a definition may result in assigning undue clinical significance to EEG and other changes that may be normal physiological responses with no adverse clinical effects. This may lead to unnecessary treatment in many patients. Second, 20% to 30% of respiratory events terminate without arousals that meet the standard definition (22, 58, 201, 257, 296). Even when the definition of cortical arousals is relaxed to include high frequency shifts greater than 1 s (instead of > 3 s), and a change in sleep stage to a lighter stage (e.g. N3 to N2), 22% of respiratory events are still found to end without cortical arousals (58). To attribute these openings to unseen arousals without credible scientific support does a major disservice to scientific efforts that aim to find alternative (to mechanical) therapies for OSA. This is because such interpretation is essentially a denial of the existence of potentially effective compensatory mechanisms that can open the airway without arousal and which can be exploited for alternate, to CPAP, therapy.

The only evidence that subcriterion arousals are clinically significant comes from a study that utilized auditory stimuli adjusted to increase heart rate or blood pressure (autonomic response) without EEG changes that meet the standard definition (146). In this study, subjects had shorter sleep onset latency on multiple sleep latency test the day following the fragmentation night (6.2 vs. 8.0 min; $P = 0.01$). There was also a marginal reduction in maintenance of wakefulness test (MWT) (25.7 vs. 29.0 min; $P = 0.04$) and a marginal deterioration in a test of mood ($P = 0.03$). While this is suggestive, it is important to note that cortical changes were not absent in this study. Rather, they simply did not meet the standard definition. In fact, the same authors (146) found significant changes in EEG by fast Fourier transformation and there were other visible changes that were not scored as arousals because they did not meet the 3-s rule. The changes in daytime sleepiness and mood observed with this "nonvisible" sleep fragmentation (146) were considerably less than those observed by the same authors when the auditory tone was sufficient to produce cortical changes that met standard arousal definition (144). Thus, the effect of cortical changes on cognitive function is graded. If one extrapolates this difference in outcome (sleepiness, mood) between cortical changes that meet standard criteria and those that do not, back to the case where there are no cortical changes at all, it is almost certain that stimuli that are not associated with any cortical changes would not be associated with significant cognitive impairment.

In summary, while the complications of arousals that meet the AASM criteria are well established (52, 68, 144, 203), the evidence that subcriterion arousals impair cognitive function is suggestive at best and, if the definition of cortical arousals is relaxed somewhat to include changes greater than 1 s (instead of > 3 s) and/or power spectral shifts, stimuli not associated with cortical arousals are likely to have no effect on cognitive function.

With respect to the mechanism of upper airway opening at the end of events, there is no reason to believe that any of the changes attributed to subcriterion arousals are due to anything other than normal physiological responses to the stimuli

produced by the obstructive event. The main evidence in support of "arousal" at the end of apneas in the absence of cortical arousals is the increase in heart rate and blood pressure (as directly measured or as inferred from reduction in pulse transit time) that occur *after* upper airway opening (194). While bona fide arousals are associated with increases in heart rate and blood pressure, increases in heart rate and blood pressure during sleep do not necessarily reflect arousals. Heart rate and blood pressure change routinely with every breath during sleep (sinus arrhythmia) and spontaneously in association with the pure K complexes of Stage N2 (234, 238, 256) and for no apparent reason throughout sleep, particularly during REM sleep (234). It is not clear why such changes are viewed as consistent with sleep, but when they occur at the end of an obstructive event they must reflect a state change (arousal). At the end of an obstructive event ventricular afterload decreases as intrathoracic pressure increases (from more to less negative). This inevitably results in a sudden increase in cardiac output, which is normally (physiologically) met with increases in heart rate and blood pressure. To say that such a response is indicative of arousal is clearly unreasonable. It is also unreasonable to interpret the occurrence of a run of delta waves near upper airway opening as arousal without evidence that these waves are different from the delta waves or K complexes found in normal sleep (stages N2 and N3). In fact, as suggested by Svanborg and Guilleminault (249), it is quite possible that these reflect an attempt by the brain to avoid arousal through rapid progression to deep sleep. With the aforementioned discussion, we do not imply that the hemodynamic changes that occur during and following respiratory events are not clinically significant. Rather, we simply indicate that in the absence of cortical arousal these changes should not be attributed to a state change.

The other evidence that is occasionally used to support the concept of subcriterion arousal when opening occurs without visible cortical arousal is the occurrence of chin EMG bursts near upper airway opening in association with K-complexes or delta waves (257). However, the chin EMG leads do pick up GG activity. Thus, the occurrence of chin EMG activity near upper airway opening, particularly when in phase with inspiration, may simply reflect physiological recruitment of the GG.

Finally, recruitment of the TP muscle at the time of opening was recently listed by Jordan et al. (105) as supporting the occurrence of arousal in cases where there was no visible cortical arousal at opening. The rationale here was that TP responds poorly to mechanoreceptor and chemical stimuli during sleep. The work cited in support of this statement (141) was performed on normal subjects in whom pharyngeal pressure could not be reduced much without arousal [average maximum negative pressure tested was –9.2 cmH_2O (141)]. With this level of stimulation, even the GG did not respond in half the subjects (141). Other studies have shown that the TP responds to negative pressure in dogs (5) and in humans (278). Furthermore, the average TP responses reported in Jordan's study (Fig. 2 in reference 105) had the same temporal profile as that of the GG. Thus, recruitment of TP in the course of obstructive events need not indicate arousal.

Another issue that relates to this topic is whether lack of cortical changes in standard central and occipital electrodes is enough to rule out cortical arousal. O'Malley et al. (170) reported that the addition of frontal electrodes increases the number of identified cortical arousals. Others could not confirm this finding (146). Furthermore, in the O'Malley study changes were present in the standard leads but they simply did not meet the 3-s rule.

Given the above considerations, it is suggested that, in the setting of OSA, the term arousal be restricted to the presence of a shift to higher frequencies in the EEG that is not a spindle and lasts more than 1 s, as documented visually or by power spectral analysis. This is the definition that will be used in the remainder of this discussion on arousals. As a corollary, upper airway opening events not associated with such cortical changes will be considered as having been mediated by nonarousal, conventional physiological responses.

Respiratory stimuli that cause arousal

This topic has been reviewed extensively by Berry and Gleeson (22). Hypercapnia (30, 59, 85), hypoxemia (31, 78, 85), and inspiratory resistive loads (77) can be tolerated up to a certain level, above which the subject arouses. Gleeson et al. (77) determined the peak negative esophageal pressure just before arousal when arousal was induced by hypoxemia, hypercapnia, and inspiratory resistive load in normal subjects. They found that the esophageal pressure at which arousal occurred was the same in all three conditions. This finding led to the unifying concept that the primary respiratory stimulus for arousal is peak negative intrathoracic pressure (77), most likely acting via chest wall receptors (including muscle receptors). In the presence of upper airway obstruction, upper airway mechanoreceptors may also contribute, although the evidence for this source of input is not conclusive (22).

The notion that the intrathoracic pressure deflection is the main arousal stimulus was subsequently validated in OSA patients by showing that peak negative esophageal pressure just before apnea termination (with arousal) was the same whether the subject breathed air, hyperoxic, or hypercapnic mixtures (26, 27, 114). Gas mixtures simply alter the time it takes to reach the threshold pressure (arousal threshold).

What is the respiratory arousal threshold?

Most information on arousal threshold was obtained by measuring the maximum negative deflection in esophageal or supraglottic pressure (22). In the setting of OSA, changes in pharyngeal pressure below the site of obstruction reflect changes in intrathoracic pressure since there is either no flow (apnea) or a fixed low flow (hypopnea), thereby resulting in no, or fixed, pressure difference between the pharynx and alveoli. When measured in this way, arousal threshold in normal

subjects ranges from 10 to 30 cmH_2O (21, 26,27,28, 77, 102), while in OSA patients it can be as high as 80 cmH_2O (25, 116). Arousal threshold varies considerably from time to time during the night (20), presumably because of changes in depth of sleep [delta power (20, 25, 296)]. For this reason, it is necessary to measure the threshold repeatedly during different sleep stages and express the threshold as an average for the patient. Arousal threshold has been shown to increase with ethanol (21), sedatives (25,28,61,80,88,181,302), sleep fragmentation (22), and by untreated OSA (24, 35, 82, 135).

Role of arousals in the pathogenesis of OSA

The role of arousals in OSA has been highly controversial, with arousal getting credit as the only way to open the obstructed airway during sleep (202) and, by extension, to save the life of the patient, to being considered as an unnecessarily sensitive defense mechanism that is responsible for the development of OSA in a majority of patients (296). A brief historical review will explain this paradox.

In 1978, Remmers et al. published their classical paper on the pathogenesis of OSA (202). These authors observed that during the obstructed phase GG activity increased and esophageal pressure decreased (more inspiratory effort) but the upper airway remained closed until there was a disproportionate increase in GG activity, associated with cortical arousal. To explain this, they proposed that while the increase in chemical drive activates the GG, which tends to open the airway, this increase in dilating force is counteracted by the concomitant increase in suction pressure from the diaphragm, which opposes opening. They concluded that the "balance of forces" remains in favor of obstruction until there is an arousal-mediated disproportionate increase in GG activity (202).

In the era of the Remmers' study (mid-late 1970s) patients subjected to sleep studies were principally those who suffered what we now call the "obesity-hypopventilation syndrome" (OHS). Remmers' patients were no exception (202). Their BMI was 41 $\pm$ 10 $kg.m^{-2}$ (range 33-64), their daytime P_aCO_2 was 47.1 $\pm$ 5.1 mmHg, their daytime P_aO_2 was 66 $\pm$ 16 mmHg, and they were somnolent. The "balance of forces" mechanism and its dependent conclusion, that arousal is needed to open the airway, were instantly accepted then.

While these conclusions likely still apply to patients with OHS, in the 33 years that have elapsed since this study (202) the type of patients being diagnosed with OSA has changed dramatically. OHS represents a small minority of patients diagnosed with OSA now. The vast majority of current patients have normal daytime P_aCO_2, develop relatively brief obstructive events [average 18.1 $\pm$ 10.6 s (296)], during which the decrease in SpO_2 is relatively modest (decreases to $< 80\%$ are infrequent), and do not develop sustained hypoxemia or hypercapnia during sleep. The control of breathing in these patients is clearly different from that of patients with OHS.

In view of the dramatic changes in the type of patient currently diagnosed with OSA, and in light of recent findings, the role of arousals has undergone substantial revisions:

1. *Are arousals needed to open the airway?* Several investigators had pointed out earlier that some obstructive events terminate without an apparent cortical arousal (22, 58, 201, 257). Not much attention was given to these and they were simply attributed to arousals occurring elsewhere in the brain. However, Younes (292) found that 78% of patients, most of whom had moderate/severe mechanical abnormalities, had periods of stable sleep and breathing (no hypopneas/apneas/arousals for > 3 min) in the same body position and sleep state (REM vs. NREM) associated, at other times, with recurrent OSA (e.g. Fig. 18). Development of stable breathing periods could not be accounted for by spontaneous variation in severity of anatomic abnormality (292). Clearly, a continuously open airway for more than 3 min cannot be mediated by a hidden arousal. This observation indicated that most patients are capable of recruiting enough dilator activity to overcome the mechanical abnormality without the benefit of arousal, at least some of the time.

   The other important evidence in this respect was obtained from examination of the temporal relation between the onset of arousal and the time of upper airway opening in 82 OSA patients in whom presence or absence of arousal at the time of opening was determined by visual inspection (high frequency shift > 1 s) and by power spectral analysis of the EEG (296). In cases where there was no cortical arousal, heart rate at the time of opening was found to be significantly lower than in the preceding two inspirations. Since the increase in heart rate typically precedes arousal by one or two beats (225), the finding that heart rate was slower at the time of opening further supported the absence of arousals in such cases. There were no arousals before or after upper airway opening in 17% of events (Type 1; Fig. 28). In 22% of events, opening occurred first but was

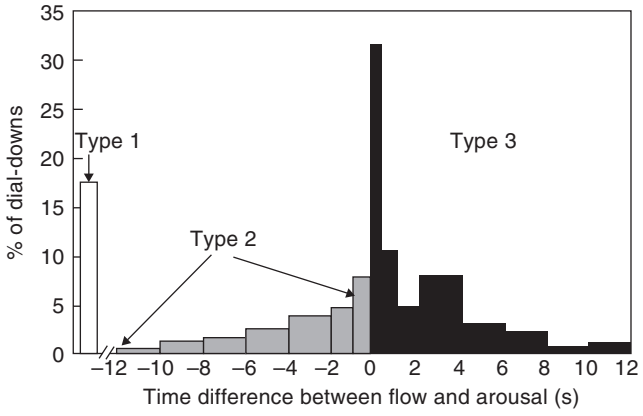

Figure 28 Frequency of observations having different intervals between upper airway opening and arousal. Type 1, no arousal before or after opening. Type 2, opening occurred before arousal. Type 3, opening occurred at or after arousal. Adapted, with permission, from reference 296.

followed by arousal 0.5 to 12.0 s later (Type 2), while in the remainder (61%) arousal started at or before (up to 12 s before) opening (Type 3, Fig. 28). Figure 28 shows the frequency distribution of time intervals between upper airway opening and onset of arousal. Although there was a clear peak at time 0, the arousal started before or after opening, or did not occur at all, in nearly 70% of cases. More importantly, there was no consistent relation between opening and arousal onset within the same patient, with the patient showing different types at different times in the same study. Because the relationship between arousal and opening was not constant in the same patient, this time difference could not have been due to technical factors such as electrode position. With more severe obstructions, the frequency of Type 1 decreased and that of Type 3 increased (296). Furthermore, as EEG delta power increased, the frequency of Type 1 increased and that of Type 3 decreased (296).

These kinds of relations are not consistent with a cause effect relation (i.e. arousal resulting in opening). Rather, they suggest that in OSA patients the stimulus intensity (inspiratory effort) required to cause arousal is, on average, in the same range as that required to recruit enough dilator activity to open the airway (296). When more activation is required to open the airway (high dilator opening threshold, Fig. 26), the arousal threshold is more likely to be reached sooner, and vice versa. Likewise, when arousal threshold is high (e.g. high delta power), dilator opening threshold is more likely to be reached before there is an arousal (Fig. 26).

Thus, it is clear that in the majority of OSA patients, reflex (i.e. nonarousal related) mechanisms are capable of opening the airway and keeping it open.

2. *How much do arousals advance upper airway opening?* The latency to upper airway opening in Type 2 events (arousal occurring after opening) was not different from the latency to opening in Type 3 events. However, arousal occurred, on average, 5 s later (296). This suggests that, on average, when arousals occur first, they advance opening by only a few seconds, if at all. This possibility was confirmed in a more recent study where GG activity was recorded during CPAP dial-downs in OSA patients (298). In observations terminated with arousal, GG activity had increased spontaneously prior to arousal to within 5.4 ± 4.6% GG_{MAX} of the value required for airway opening. The arousal-free rate of rise of GG activity in the vicinity of airway opening was 8.6 ± 5.2% GG_{MAX} per breath. Thus, if arousal had been delayed by, on average, a few seconds, GG activity would have risen spontaneously to the required level.

The obvious conclusion here is that, all else being the same, in most patients upper airway opening would not be delayed much if arousal threshold were to increase. This conclusion obviously does not apply to a minority of patients in whom dilator activity is unresponsive to large increases in chemical drive (136). In these patients, arousal could potentially prevent severe deterioration in blood gas tensions.

3. *Are arousals protective*? Clearly, when an arousal terminates a long apnea during which SpO_2 decreased to a dangerous level, or in cases where there is hypoventilation during sleep (OHS), the arousal was protective in that it prevented potentially serious deteriorations from happening. However, as indicated before, this type of patient is not common among patients currently diagnosed with OSA. In his 2004 study (296), Younes reported that the interval between dial-down of CPAP and event termination with arousal was 18.0 ± 10.6 s. Considering that blood gas tensions (including mixed venous tensions) were normal on CPAP prior to the onset of the obstructive event, arterial PCO_2 could not have increased much during the event, which was in all cases less than the recirculation time. SpO_2 also decreased by only a few precent. Younes concluded that, notwithstanding the fact that arousal threshold is higher in OSA patients than in normals (22), arousal threshold remains quite low such that in the majority of patients currently being diagnosed with OSA arousals occur at quite unthreatening levels of blood gas tensions (296). This conclusion is also supported by the fact that in most OSA patients SpO_2 only infrequently decreases below 70%. Particularly when considering that the arousal was in response to the SpO_2 that existed 7 to 10 s (lung to carotid circulation time) before the nadir of SpO_2, in most patients, arousal occurs before SpO_2 has reached 85%. Clearly, if arousal were not to happen, allowing reflex mechanisms to open the airway, a further lengthening of the event by a few seconds (see point 2, earlier) would not present a significant threat.

The arousal threshold in OSA patients has been directly measured in several recent studies. Using inspired mixtures with different CO_2 and O_2 concentrations, Younes et al. (300) determined the level of ventilation preceding arousal in 21 patients with severe OSA (AHI 91 ± 24 h^{-1}; overnight minimum SpO_2 74 ± 2.9%). Ventilation preceding arousal was 212 ± 54% of the eupneic V_E on air (range 140-382% baseline). On average, arousal occurred when V_E had increased ≈ 8 $L.min^{-1}$ above eupnea (range 2.5-20.0 $L.min^{-1}$). These levels of ventilatory stimulation occurred when $P_{ET}CO_2$ had increased 3.3±2.2 mmHg above baseline (air breathing on CPAP) and SpO_2 had concurrently decreased 3.7 ± 1.6% below baseline (300). Thus, although in a few patients arousal threshold was high, in the majority of these OSA patients, the changes in gas tensions that triggered arousal were clearly nonthreatening. Heinzer et al. (88) determined the $P_{ET}CO_2$ at arousal when inspired CO_2 concentration was increased in OSA patients (AHI 52 ± 32 h^{-1}) while on CPAP. It was 49.8 ± 4.8 mmHg. The authors did not report the baseline $P_{ET}CO_2$ on CPAP. However, assuming it was normal (≈ 43 mmHg) and considering that their stimulus was pure hypercapnia, the results are consistent with the Younes et al. study (300) in

showing that arousals are triggered with a minimal chemical stimulus in most OSA patients. In two recent studies, arousal threshold was determined from the esophageal or pharyngeal pressure deflection just preceding arousal during obstructive events (61, 88). In one study [AHI 52±32 h^{-1} (88)], the arousal threshold was 16.9 ± 6.3 cmH_2O (range 11-29 cmH_2O). In the other study (61), the arousal threshold was 15.6 cmH_2O (range 7-45 cmH_2O) in 17 patients with AHI of 31 ± 5 h^{-1} and overnight saturation nadir more than 70%. These arousal threshold values are well below what was reported in the earlier literature [40-80 cmH_2O; (24, 114, 267, 284)], further supporting the conclusion that in most patients currently diagnosed with OSA the arousal threshold is unnecessarily low. In fact, these recently determined arousal thresholds are, on average, not that different from those reported in normal subjects (26,27,28), where the esophageal pressure deflection at eupnea (first obstructed breath) is 10 to 13 cmH_2O and increases to ≈ 20 cmH_2O just before arousal.

In summary, there is compelling evidence now that in most OSA patients arousal occurs with minimal, nonthreatening changes in blood gas tensions and, accordingly, that in such patients with low arousal threshold some delay in arousal should present no harm and may give the reflex mechanisms the opportunity of progressing to the point where the airway is opened without arousal.

4. *Do arousals promote instability?* Arousals can, theoretically, increase the postevent ventilatory overshoot by producing a more complete airway opening [thereby reducing the impedance term in the LG equation (equation 1, above)] as a consequence of excessive activation of the dilators. A greater overshoot would result in a greater improvement in blood gas tensions, removing the stimulus for dilator activation and setting the stage for another obstruction upon resumption of sleep (296, 297). Younes reported that the magnitude of the postevent ventilatory overshoot increases progressively as arousal intensity increases (296).

However, more recently, Jordan et al. (105) found that when events with and without arousal were matched for severity and duration (105) there was no difference in the magnitude of the overshoot. It is, therefore, possible that the positive relation between arousal intensity and the magnitude of the overshoot in the Younes study (296) was fortuitous. Thus, it may be that a higher chemical drive at the time of opening (e.g. because of a different arousal threshold) was responsible for both the higher arousal intensity and the greater overshoot forcing a correlation between arousal intensity and the overshoot. However, it must be pointed out that the obstructive events in the Jordan study (105) consisted only of mild hypopneas, whereas in the Younes study (296) the events were predominantly apneas or severe hypopneas. The authors also did not comment on the intensity of arousals. It is possible that arousal intensity at the end of these mild hypopneas was low. Younes found only a minimal increase in the overshoot with low intensity arousals (296). More studies are needed to determine whether arousals independently result in a greater overshoot.

Regardless of the effect of arousals on the overshoot, termination of events via the arousal mechanism is destabilizing if the arousal threshold (T_A) is below the T_{ER} (see Fig. 26). This is because, in such a case, arousal will occur before chemical drive and, by extension, dilator activity has reached a level that can open the airway reflexively. Under such conditions, there is little possibility for chemical drive to increase further and the obstruction would recur as soon as sleep resumes. When T_A is less than T_{ER} but both are very high, the instability is an acceptable price to pay for safety; without arousal, deterioration in blood gas tensions may be severe. However, when both thresholds are low, premature occurrence of arousal destabilizes breathing for no good reason.

Another consideration here is the possible effect of arousal on STP. As indicated earlier, one of the manifestations of STP is that at the same chemical drive, dilator activity after an obstructive event is higher than before the event (after discharge; Figs. 24 and 26). Persistence of high activity despite the reduction in chemical drive may help prevent recurrence of the obstruction. It is not clear whether the occurrence of an arousal at the end of an event promotes more or less after-discharge. In sleeping, freely behaving rats sleep is highly fragmented with very short interarousal intervals (302). With short intervals, there is little or no baseline dilator activity (302). When the interarousal interval is longer (spontaneously or by use of sedatives) baseline dilator activity increases gradually in a ramp-like fashion between arousals (181, 302). This increase in dilator activity occurs while diaphragm activity remains unchanged, indicating that it is not due to a progressive increase in chemical drive or mechanical load (302). As soon as an arousal occurs, this high baseline activity is reset to a very low level, only to start increasing again later (302). Although the mechanisms may be different, both STP and the slowly evolving activity ramps in the sleeping rat are examples of time-dependent recruitment of pharyngeal dilators. If arousal inhibits STP, that would cause further instability. This issue needs further investigation.

A more direct approach to determining whether arousals are destabilizing is to study the effect of sedatives on the extent of instability in OSA patients (e.g. the AHI). There is much anxiety about the use of sedatives in OSA primarily because of the common clinical experience that patients with compromised upper airway often develop OSA upon administration of sedatives, and an early report that subanesthetic doses of pentobarbital inhibit dilator activity in decerebrate cats (96). However, these observations are based on comparison between an awake state (prior to drug administration) and drowsy or sleeping state following drug administration. Under these conditions, the development of OSA in humans, or inhibition of dilator activity in decerebrate animals, may well be due to reduced level of vigilance as opposed to drug related inhibition of the dilators. Recent studies have clearly

shown that when dilator activity is compared *during* sleep before and after sedative doses of pentobarbital (63, 302) or benzodiazepines (181), dilator activity is, in fact, higher after drug administration. Furthermore, Eikerman et al. (63) found that in normal subjects, sedative doses of pentobarbital did not inhibit the negative pressure reflex during wakefulness or impair dilator responses during sleep and, when obstructions were induced by lowering airway pressure during sleep, GG activity increased to a higher level before arousal occurred.

These observations have encouraged clinical trials of the effect of sedatives on the AHI in OSA. The first such trial was recently published (61). Eckert et al. (61) measured the AHI before and after administration of a standard dose of eszopiclone, a nonbenzodiazepine sedative, in OSA patients in whom SpO_2 was more than 70%. There was a significant reduction in AHI in patients with arousal threshold less than 15 cmH_2O (from 25 to 15 h^{-1}) but not in those with a higher arousal threshold (61). Although these results are encouraging, there are several theoretical and practical considerations that would make it unlikely that sedatives, *per se*, would become an effective treatment except in a minority of OSA patients:

First, sedatives can obviously not be used in patients with long apneas and major decreases in SpO_2 (i.e. those with a high arousal threshold).

Second, currently available sedatives, when used in therapeutic doses, increase arousal threshold only slightly. Eckert et al. found that eszopiclone increased arousal threshold from 14 to 18 cmH_2O in OSA patients (61) and Berry et al. found that triazolam increased arousal threshold from 20 to 26 cmH_2O in normal subjects (28) and from 45 to 53 cmH_2O in severe OSA patients (25). Thus, these increases in arousal threshold are expected to be effective in only a minority of patients in whom not only is the arousal threshold low, but also the chemical drive required to open the airway without arousal (T_{ER}) is quite low. This combination is not common (300). Giving higher sedative doses to increase arousal threshold more is not practical in view of the side effects of these medications.

Third, it is not clear that eliminating arousal will necessarily enhance stability and reduce OSA severity. The intended effect of eliminating arousals is to allow the reflex mechanisms to evolve to a higher level and open the airway without arousal (296, 297). However, by doing so, the chemical drive at the time of arousal will necessarily be higher. A large overshoot produced by arousal may simply be replaced by a large overshoot produced by a higher chemical drive. Recurrent obstructive events without arousal are often seen during polysomnography, albeit much less frequently.

Fourth, given that the factors that affect stability (basic LG, arousal threshold, T_{ER}), as well as drug levels, may vary considerably from time to time and from one night to the other, it may be expected that sedatives may be effective at some times, or in some nights, but not in others. Such unpredictable results would not be clinically acceptable.

Effective Recruitment Threshold (297, 300)

Definition

T_{ER} is the increase in chemical drive, above eupnea, required to activate the dilators enough to open the airway without arousal.

How T_{ER} influences ventilatory stability

How much chemical drive must increase above eupnea before the airway opens via nonarousal mechanisms (T_{ER}; Fig. 26) is the most important variable that determines stability in OSA patients (297). When T_{ER} is high, there is a greater likelihood that the arousal threshold will be reached first (Fig. 26). If arousal occurs first, there is no possibility for chemical drive to rise to T_{ER}, and obstruction will recur as soon as the arousal ends. Even without arousal, a high T_{ER} inevitably means that inspiratory intrathoracic pressure will be quite negative at the time of opening, and this should increase the likelihood of a large ventilatory overshoot.

Range of values

T_{ER} was first measured by Younes et al. (300). In approximately half the patients, it was greater than the arousal threshold. Under these conditions, T_{ER} cannot be measured precisely but can be expressed as more than arousal threshold. Arousal threshold in these patients ranged from 50% to 180% increase in respiratory drive above eupnea (i.e. equivalent to 150%-280% of eupneic drive). In the other patients, in whom it was below arousal threshold, it ranged from just above eupneic drive to 210% of eupneic drive. Thus, T_{ER} varies over a wide range among OSA patients, from being just above eupneic drive to more than 280% eupneic drive.

Factors that determine T_{ER}

Figure 26 shows the factors that determine T_{ER}. By definition, patients with OSA develop obstructive events because the baseline dilator activity at sleep onset (or upon resumption of sleep) is less than the activity required to keep the airway open. Once an obstructive event develops, it will persist until dilator activity increases enough to open the airway, via arousal or nonarousal mechanisms. The increase in dilator activity, above baseline, required to open the airway has been termed dilator opening threshold (Fig. 26). Therefore, T_{ER} is determined by how high the dilator opening threshold is and the response of the dilators to increasing chemical drive (directly or indirectly via more negative pharyngeal pressure).

Dilator (GG) opening threshold

GG opening threshold was recently measured in 32 OSA patients (AHI 74 $\pm$ 42 h^{-1}) (298). The method of measurement

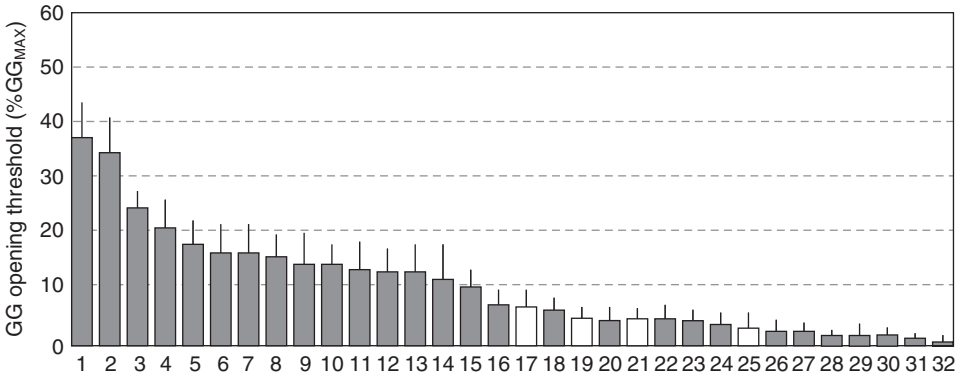

Figure 29 Average genioglossus (GG) opening threshold, expressed as % maximum GG activity, in 32 patients arranged in order of threshold values. Bars are standard deviation. Open bars are patients with closing pressure less than −1 cmH2O. Adapted, with permission, from reference 298.

is illustrated in Figure 21. It averaged only 10.4% GG_{MAX} above baseline but there was a very wide range (0.3%-37.7% GG_{MAX}; SD 9.5% GG_{MAX}; Fig. 29). Interestingly, the absolute level of GG activity at which the airway opened was the same whether or not there was an arousal at the time of opening (12.4 ± 10.6 vs. 12.1 ± 11.6% GG_{MAX}). Thus, it is not important what mechanism activates the dilators.

Although, as may be expected, GG opening threshold was quite low in patients who developed only hypopneas upon dial down of CPAP (P_{CRIT} < −1 cmH_2O; 2.8 ± 2.3 vs. 12.9 ± 9.7 % GG_{MAX} in patients with a positive P_{CRIT}), there was, surprisingly, no correlation between GG opening threshold and P_{CRIT} when P_{CRIT} was more than −1 cmH_2O [Figure 30; (298)]. This likely explains the poor correlation observed previously between P_{CRIT} and the effective CPAP level (227) and suggests that when a complete obstruction develops, factors other than the passive recoil of the pharynx play the dominant role in determining how much dilator activity is required to open the airway. These factors possibly include (298):

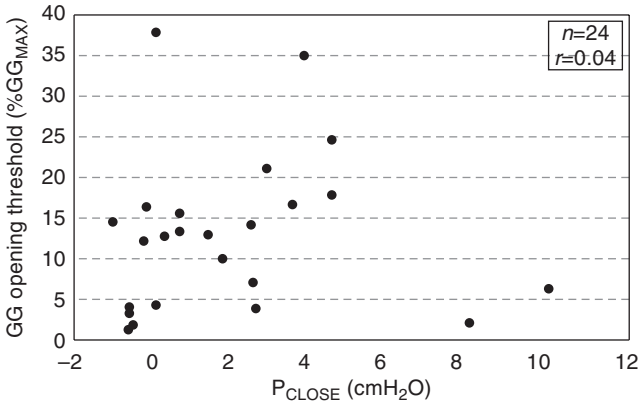

Figure 30 Relationship between genioglossus opening threshold and closing pressure (P_{CRIT}) in patients with P_{CRIT} more than −1 cmH2O. Adapted, with permission, from reference 298.

(a) Differences in dilator muscle strength: A weaker muscle requires a greater %MAX activation to generate the same force. Maximum tongue force varies considerably among OSA patients and normal subjects [range 15-43 Newtons (161)]. In addition, there is the possibility of myopathy in some OSA patients (see section on apnea leading to more apnea).

(b) Differences in site of obstruction: it is possible that, for the same P_{CRIT}, a retroglossal obstruction can be more easily overcome than a retropalatal obstruction, since the latter would be influenced only indirectly by tongue contraction. The site of obstruction varies among OSA patients from retropalatal to retroglossal (45, 93, 232).

(c) Differences in viscosity of pharyngeal secretions: surface tension of pharyngeal lining fluid varies among OSA patients and normal subjects [45-65 mN/m (117, 118)]. Tenacious salivary secretions should make it more difficult to open the airway from a closed position. In support of this, reducing surface tension of pharyngeal secretions with surfactant was associated with a reduction in the luminal pressure required to open the airway (116,262), and reduction in the AHI (104, 117, 160).

(d) Differences in balance of forces: the increase in GG activity during obstructive episodes is associated with a greater negative pharyngeal pressure that tends to oppose opening (202). The latter is a consequence of increased respiratory drive. According to one construct (202), opening from a completely closed position can only occur when the dilating force produced by tongue activation exceeds the opposing force produced by negative pharyngeal pressure. It is possible that differences in pharyngeal anatomy or physical characteristics of the tongue alter the relationship between negative pharyngeal pressure and the collapsing backward force it exerts on the tongue. Such differences would translate into greater or lesser activity required to dislodge the tongue from a closed position.

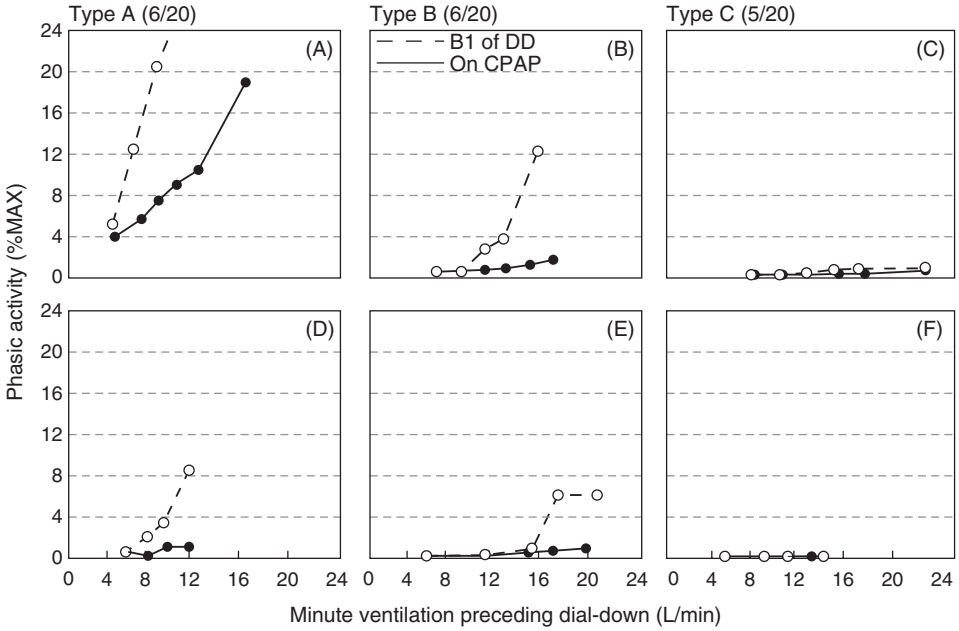

Figure 31 Response of phasic genioglossus activity to increasing chemical drive on CPAP (solid lines) and during the first obstructed breath in six patients representing the three response types. Type A response (panels A and D): mechanoreceptor effect (difference between the two lines) is evident beginning with baseline (lowest) drive. Type B response (panels B and E): mechanoreceptor effect appears only after a threshold increase in chemical drive. Type C response (panels C and F): no mechanoreceptor effect across the entire range of chemical drive permitted by the arousal threshold. Adapted, with permission, from reference 136.

It should be noted that all mechanical devices and surgical interventions currently used in the treatment of OSA operate by reducing the amount of dilator activity required to keep the airway open (dilator opening threshold). In the extreme, optimal CPAP reduces GG opening threshold to zero. The finding that GG opening threshold is affected by factors other than passive collapsibility should present opportunities for further investigation of these factors with a view to developing alternate approaches to therapy (298). It should also be pointed out that, by increasing baseline activity, particularly tonic activity, STP reduces dilator opening threshold (Fig. 26). Thus, investigations into mechanisms of STP and how to enhance it may also open new avenues for therapy.

Response of pharyngeal dilators to increasing chemical drive

This topic has been discussed earlier. It was pointed out that the GG does not begin responding to increasing chemical drive or to negative pharyngeal pressure until a threshold increase in chemical drive, above eupnea, has occurred (Figs. 22 and 23; dilator recruitment threshold, Fig. 26). This recruitment threshold varies considerably among patients. Figure 31 (136) illustrates this spectrum. The left two panels show the response in two patients with a very low threshold; activity begins increasing as soon as chemical drive increases above eupnea. The middle two panels illustrate the response in two patients in whom chemical drive had to increase a finite amount before there was any response (Top: 2 L.min^{-1} and bottom: 10 L.min^{-1}). In the right panel there was no response up to arousal, even though chemical drive had reached three times eupneic values before arousal. Figure 31 also shows that beyond the recruitment threshold GG activity increases at different rates in different patients in response to further increases in drive (0.3%-3.4%GG_{MAX} per L.min^{-1} increase in predial-down $\dot{V}_E$ (136).

Integrated Response to Obstructive Events During sleep

How mechanical abnormalities and control mechanisms interact to determine the form and severity of OSA

Reference has been made to the fact that the relation between severity of the mechanical abnormality in the pharynx (P_{CRIT} or $\dot{V}_{MAX}0$) and polysomngraphic severity is weak at best and, accordingly, that other factors largely determine the polysomnographic consequences of the mechanical abnormality. As reviewed earlier, the main factors that fashion the response to a narrower, more collapsible pharynx, include:

(a) The ability to increase Inspiratory Duty Cycle (T_I/T_{TOT}).

(b) Unloaded flow demand of the patient (PUF).

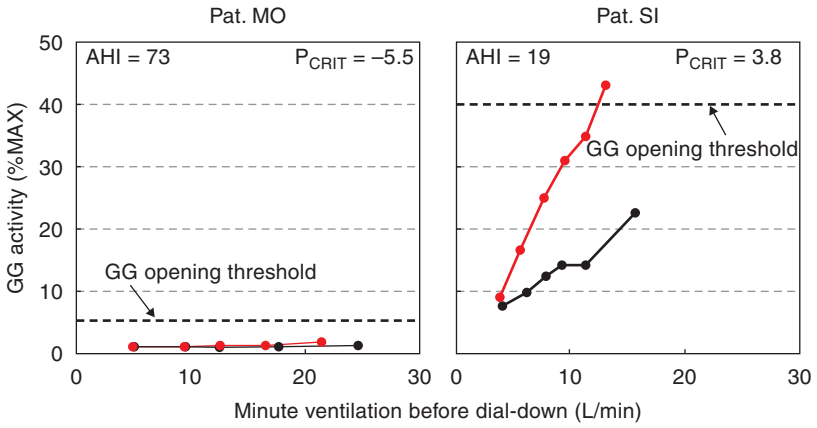

Figure 32 Two examples illustrating the importance of control mechanisms in determining the apnea-hypopnea index (AHI). Patient MO had a very high AHI despite a very low critical closing pressure (P_{CRIT}) and a very low genioglossus opening threshold. In this patient, the problem was that the dilators were not responsive to chemical drive up to five times the eupneic drive (i.e. very high dilator recruitment threshold). By contrast, patient SI had a low AHI despite very high P_{CRIT} and dilator opening threshold. In this patient, there was a vigorous dilator response, with activity reaching the opening threshold with a modest increase in drive. Unpublished observations.

(c) Basic chemical control loop gain (basic LG).

(d) Arousal threshold (T_A).

(e) T_{ER}, which in turn is determined by the dilator opening threshold, the dilator recruitment threshold, and the response of dilators to increasing drive beyond the recruitment threshold (Fig. 26).

We have also indicated that each of these factors varies over a very wide range among different OSA patients. Furthermore, these factors are quite independent from each other, so that the underlying mechanism(s) for instability may vary considerably from one patient to another (300). For example, Younes et al. measured Basic LG, T_A, and T_{ER} in 21 patients with severe OSA (300). They found no correlation between T_A and T_{ER} and a weak correlation between T_A and basic LG. In some patients, the instability was primarily due to high T_{ER} while in others it was due to a combination of low TA and high basic LG, and so on. Figure 32 shows extreme examples of how these responses can influence polysomnographic severity. Patient MO had mildly abnormal mechanics (P_{CRIT} –5.5 cmH_2O) and needed very little recruitment of dilators to open the airway (GG opening threshold = 5% GG_{MAX}). His arousal threshold was also very high, as he tolerated a 5-fold increase in eupneic drive ($\dot{V}_E$ increased from 5 to 25 $L.min^{-1}$ before he aroused). These are all very favorable numbers. However, his GG recruitment threshold was very high (there was no increase in GG activity during the hypopneas despite a 5-fold increase in eupneic drive). Therefore, his T_{ER} was very high and higher than T_A. As a result his AHI was 73 h^{-1}. By contrast, patient SI had very poor mechanics (P_{CRIT} 3.8 cmH_2O) and needed marked increases in GG activity to open the airway (40% GG_{MAX}). Yet he was able to reach the GG opening threshold with only moderate increases in chemical drive. His AHI was only 19 (i.e. he had plenty of stable periods).

Figure 33 is a flow chart that summarizes how different control mechanisms determine the response to the primary anatomical problem and, hence, the polysomnographic features. This figure and the related text mentioned later were published in a recent review (297) and are inserted here with minimal changes.

At the top of the chart (Fig. 33), the anatomical defect is not expressed in absolute terms (i.e. P_{CRIT} or $\dot{V}_{MAX}0$) but as the relation between the anatomical defect (quantified by $\dot{V}_{MAX}0$) and the individual's flow demand. This is to emphasize that the same anatomical defect may or not be significant depending on the metabolic and gas exchange status. Distinction is made between $\dot{V}_{MAX}0$ being higher or lower than 30% of peak unloaded flow demand. This is because when $\dot{V}_{MAX}0$ is more than 30% peak unloaded flow (i.e. mild/moderate hypopnea at eupneic drive) compensation is possible with the duty cycle mechanism without the need to increase $\dot{V}_{MAX}$, whereas with more severe obstructions a stable response requires an increase in $\dot{V}_{MAX}$, which is a less reliable and potentially more unstable response. With milder obstructions (left side of the chart) the entire range of polysomnographic features, from no abnormality to steady flow limitation to OSA may occur, depending on T_{ER} and the potency of the duty cycle response. With more severe hypopneas and apneas, an equally wide range of manifestations may result depending on the relation between T_{ER} and arousal threshold, absolute arousal threshold, and basic LG. Regardless of the initial severity, the final responses may be normocapnic or hypercapnic, depending on the steady state response to CO_2 and hypoxia and on arousal threshold. Daytime hypercapnia may result particularly in the presence

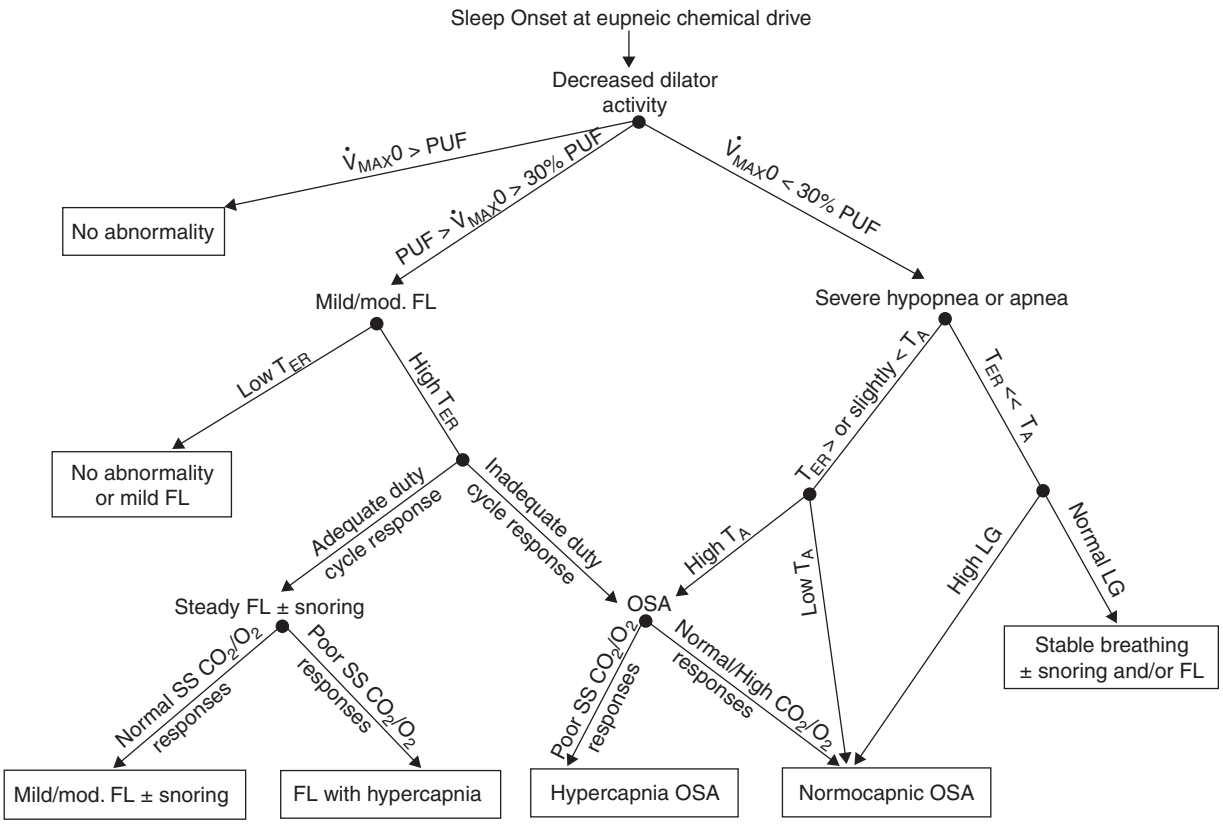

Figure 33 Flow chart showing how different polysomnographic features (boxed terms) can arise following sleep-induced obstructive events. FL, flow limitation; LG, loop gain; OSA, obstructive sleep apnea; PUF, peak unloaded flow rate; SS, steady state; TA, increase in chemical drive required to cause arousal; TER, increase in chemical drive required to open the airway without arousal; UARS, upper airway resistance syndrome; $\dot{V}_{MAX}0$, maximum flow at atmospheric pressure in the absence of pharyngeal dilator activity. See text. Adapted, with permission, from reference 297.

of comorbidities [e.g. chronic obstructive pulmonary disease (the overlap syndrome (271) or obesity-associated restrictive disorder (obesity hypoventilation syndrome (172)]. A low T_{ER} mitigates hypercapnia even when CO_2 and hypoxic responses are low, since the change in gas tensions required to increase $\dot{V}_{MAX}$ to a sustainable level would still be small. This accounts for the absence of a hypercapnic version of stable breathing on the far right of the chart (Fig. 33).

The AHI is the product of the frequency of cycling when breathing is unstable and the percentage of sleep time spent cycling (292). The frequency of cycling during unstable periods is principally determined by the rate of increase in chemical drive, and the lower T_{ER} and arousal threshold. A low cycling frequency results when the rate of rise of chemical drive is low and both T_{ER} and arousal threshold are relatively high. A low rate of rise may be a reflection of a mild ventilatory deficit resulting in a very slow deterioration of blood gas tensions. In such cases, hypopnea duration may be several minutes long and would be associated with mild blood gas tension changes, a picture currently identified as the upper airway resistance syndrome (81). On the other hand, the ventilatory deficit may be severe but the response to the chemical changes (chemosensitivity) is depressed. Here, the hypopnea may again be quite long but would be associated with severe abnormalities in blood gas tensions. In both cases cycling frequency is low, but the mechanisms, mechanical abnormalities, and clinical consequences are clearly very different. When either T_{ER} or arousal threshold is relatively low, or when rate of rise of chemical drive is high (more severe obstructions and/or high LG), such protracted (minutes) hypopnea/apneas are not possible and cycling frequency will tend to be high.

The percentage of time spent in instability, the other component of the AHI, is related to how far removed from stability the system is, relative to how much changes in the stability factors can occur spontaneously during the night. Some of the factors that determine stability change from time to time during sleep. Chief among these is arousal threshold (20). However, other factors may also change, although this needs experimental confirmation. For example, T_{ER} may be different in different body or head positions because of position-related differences in passive mechanics. Alternatively, passive mechanics may change through the night as a result of changes in vascularity or surface tension properties of the pharynx. Lung-carotid transit time may also change with cardiac function through the night. If the mechanism of instability is such that the within-night changes in stability factors cannot bring

the system to a stable state, cycling will persist throughout sleep and the AHI will equal cycling frequency. For example, if T_{ER} is sufficiently higher than arousal threshold that the spontaneous changes in arousal threshold cannot place the two thresholds in a stable relationship, there cannot be stable time. On the other hand, if the constellation of stability factors is such that the spontaneous changes that occur during the night are enough to bring the system to a stable state, cycling will occur at some times but not at others. For example, entering a deeper sleep state or a change in body or head position may abort cycling, and vice versa.

Finally, the form an obstructive event takes is related to the severity of the mechanical abnormality, the potency of the STP mechanism, and the extent of ventilatory overshoot. When passive P_{CRIT} is negative the obstructive event can only be a hypopnea. When passive P_{CRIT} is more than 0, the obstructive events may be either hypopneas, obstructive apneas, mixed apneas, or even central apneas, depending on whether the patient can develop robust STP, and whether the overshoot reduces chemical drive below T_{ER} or below central apneic threshold (Fig. 27 and related text). Another factor that may help convert apneas into hypopneas is the viscoelastic behavior of the pharynx. Thus, elastic recoil of the pharynx (i.e. collapsibility; e.g., P_{CRIT}) is least following a sustained inflation (e.g. immediately after reduction of CPAP) and increases in a time-dependent manner following removal of the inflating force (220, 292). During the ventilatory phase following an obstructive event the pharynx is maintained open for a finite period. Depending on how strongly these viscoelastic properties are expressed, collapsibility will decrease to a variable extent during the ventilatory phase and increase again later, as time passes. Such time-dependent changes in passive mechanics may delay the onset of obstruction in the aftermath of the overshoot and may, as in the case of the STP mechanism, help convert some obstructive apneas into hypopneas.

In summary, it is clear that the mechanism(s) that are primarily responsible for OSA can vary considerably from patient to patient. Because some of these mechanisms can be altered by nonmechanical interventions, and the effective interventions are mechanism specific, identifying the specific mechanism(s) responsible for instability in individual patients (phenotyping) may open the door to the use of less obtrusive therapies than CPAP. Two approaches have already been described for phenotyping patients. Younes et al. (300) used different inspired gas mixtures prior to CPAP dial-downs to determine the dynamic response to hypoxia plus hypercapnia; the arousal threshold and T_{ER} and demonstrated the heterogeneity of mechanisms in individual patients. More recently, Wellman et al. (272) used the ventilatory responses during and following sustained CPAP dial-downs that are associated with stable breathing to determine LG, arousal threshold, and the "upper airway responses" to increasing chemical drive. This latter approach assumes that dynamic LG at the onset of an obstructive event can be estimated from the ventilatory response at termination of the dial down, and that upper airway responses measured during very mild hypopneas (that can be tolerated indefinitely) can predict upper airway responses in the more severe events that occur in the complete absence of CPAP. If these assumptions can be experimentally validated, this latter approach can provide a more practical approach than that described by Younes et al. (300).

Mechanisms of apnea progression over time

There is a reasonable literature which suggests that obstructive apnea gets worse over time in both normal subjects and patients with OSA (224, 259). In some of the large longitudinal cohorts, the overall AHI increased modestly but significantly. In the Wisconsin cohort, the 8-year follow-up study showed an increase in AHI from 2.5 to 5.1 overall (168). In the Cleveland Family Study, 286 subjects who started with an AHI of less than 5 were restudied at least 5 years later. Of the 286, 26.6% progressed to mild sleep apnea (AHI of 5-15) and 10.1% to moderate to severe sleep apnea (AHI $>$ 15)(259). Studies of untreated patients with mild to severe OSA generally showed progression, although that was not always the case (18, 131, 186, 250).

In many of the studies cited earlier, an attempt was made to determine predictors of disease progression or stability. However, in general, there was little physiologic information available from which to draw meaningful conclusions. Many of the longitudinal studies reported an association between increasing BMI and increasing AHI, although there were always cases where AHI rose substantially with little to no change in BMI (18, 250). In addition, several studies reported no association between change in BMI and change in AHI (131, 186, 224). In addition, Tishler et al. (259) reported that the effect of increasing BMI on apnea severity diminished with increasing age and was minimal at ages over 60. Thus, increasing obesity is certainly not the entire explanation for increases in apnea severity over time.

Of note, there was inconsistency as to whether baseline apnea severity predicted the rate of apnea progression. Svanborg and Larsson (250) reported the largest increases in AHI in patients with initially the most severe apnea. Berger et al. (18) found the opposite, with their severe apneics demonstrating a modest, but statistically insignificant, improvement in apnea severity over time while all other groups deteriorated. Thus, whether apnea itself is leading to more severe apnea or the observed apnea progression is a product of aging and weight gain is difficult to discern from this literature. To better understand why apnea might progress over time, three areas will be addressed briefly as they relate to this topic: obesity, aging, and apnea itself.

Obesity

There is a huge literature indicating that increasing weight (as measured by BMI, waist-hip ratio, and neck size) is one of the main determinants of apnea development and severity (Fig. 2) (305). Thus, increasing obesity is certainly one of the reasons why apnea is becoming more prevalent and why it is

often progressing in severity over time in a given individual. That being said, we have less information as to why this is the case. Understanding this requires knowledge of how increasing weight affects upper airway anatomy, neural control of the pharyngeal musculature, and general ventilatory control stability.

There are likely two mechanisms by which obesity might affect upper airway anatomy/collapsibility. One would be by the simple placement of increasing quantities of fat tissue around the collapsible airway segment (hard palate to the base of the epiglottis). This has been demonstrated in several ways. First, Mortimore et al. (164) have convincingly demonstrated that patients with OSA have increased fat in the neck tissues surrounding the airway. This was the case whether the OSA patients were obese or not, although the obese OSA patients had considerably more neck fat than did nonobese OSA patients or normal controls. Shelton et al. (231) reported a direct correlation between apnea severity and the amount of fat in the tissue directly adjacent to the pharyngeal airway. They also reported a decrease in parapharyngeal fat and apnea severity with weight loss. In addition, Schwab et al. have consistently reported an increased size of the pharyngeal fat pads in OSA patients (216,218). Finally, a standard measure of pharyngeal collapsibility, P_{crit}, has been demonstrated in cross-sectional studies to increase (more collapsible) by 1.4 cmH_2O per 10 unit elevation in BMI ($kg.m^{-2}$) (221). Even greater decrements in P_{crit} have been reported following weight loss (219). Thus, obesity leads to direct deposition of fat in the tissues of the neck, making the airway more prone to collapse.

The second way in which obesity might directly affect airway collapsibility would be through reductions in lung volume. It is quite clear that substantial obesity can lead to a decreased functional residual capacity (FRC). There are also a number of studies in both animals and humans indicating that reduced lung volume leads to a more collapsible pharyngeal airway (86,179,260). This is believed to be mediated by longitudinal, tracheal traction on the airway that increases with increasing lung volume. Thus, with rising lung volume, there is greater tension on the pharyngeal walls, thereby rendering them stiffer and less likely to collapse. As obesity reduces lung volume, airway collapsibility increases.

There are no studies directly linking obesity to abnormal neural control of the pharyngeal musculature. In fact, there are studies demonstrating quite normal reflex control of the GG muscle in obese OSA patients compared to normal controls (29). In addition, Jordan et al. (106) reported very similar increases in GG EMG in obese OSA patients and nonobese controls during NREM sleep following a drop in CPAP from the optimal level. However, in the latter study, the increasing GG EMG was able to adequately restore airway patency more commonly in the normal controls than the OSA patients. Thus muscle activation may not translate into increasing wall stiffness or airway opening in obese patients as effectively as controls. This may explain the observations of Patil et al. (183), who reported a reduced ability of sustained decrements in airway pressure (which should activate upper airway muscles) to reduce pharyngeal collapsibility (passive P_{crit}) in OSA patients compared to age, sex, and BMI-matched controls. However, it should be stated that none of these studies were specifically designed to determine the effect of obesity on upper airway motor control.

Finally, the effect of obesity on ventilatory control stability (LG) is also relevant to sleep apnea pathogenesis. However, there is not a great deal of data in any OSA population clearly delineating the role of ventilatory control instability as an important modulator of apnea severity (273). There are several studies that suggest that some OSA patients may have a high LG and that this may relate to apnea severity in certain subsets of patients (301). Therefore, one can only speculate regarding the effect of obesity on LG and the effect of LG on the development of OSA in these patients. To do so, the two primary components of LG must be considered.

Plant gain could be affected by obesity due to its effect on lung volume. As stated eralier, substantial obesity is associated with reduced lung volume that would lead to decreased oxygen stores in the body and therefore increased plant gain. Controller gain could be affected by obesity in several ways. First, a subpopulation of obese patients develops the obesity hypoventilation syndrome and these patients have been found to have quite low hypercapnic ventilator responsiveness (193). Thus, controller gain would be expected to be low. However, most obese patients have a normal waking PCO_2 and normal hypercapnic responsiveness. This would be expected to yield a normal controller gain. However, to the extent obesity increases the work of breathing and the neural drive to the respiratory muscles required to yield a given increment in minute ventilation, controller gain would decrease (49). The relative contribution of these various effects on LG in obese humans remains unclear.

Aging

There is a substantial literature indicating that the prevalence and severity of OSA increases with aging (Fig. 3) (306). Some of this increase may be secondary to rising BMI with age, although this is not likely the entire explanation. The physiologic events leading to this increased apnea prevalence with aging are less clear. Thus, as was done for obesity earlier, how aging affects the variables known to be important in apnea pathophysiology will be examined, recognizing that the literature addressing this is relatively small.

Using MRI, Malhotra et al. reported a number of changes in upper airway anatomy/collapsibility with aging, several of which could render the pharyngeal airway more susceptible to collapse during sleep (139). They reported changes in the bony structure surrounding the airway, with these bones assuming a more lateral shape as the ratio of anteroposterior to lateral dimension decreased with increasing age. In addition, they reported with aging an increase in soft palate length (greater change in women than men), an increase in the length of the entire pharyngeal airway in women, and an increase in the size of the parapharyngeal fat pads (independent of BMI) in both

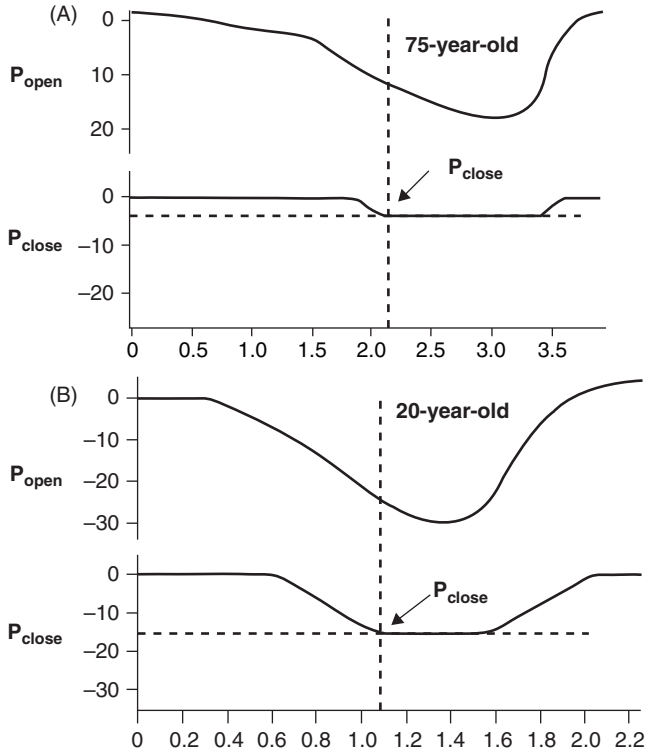

Figure 34 P_{close} as a function of age. Mean values from 18 persons. Multiple regression analysis revealed that P_{close} became less negative with age ($r = 0.75$; $P = 0.011$). Adapted, with permission, from reference 64.

genders. However, the size of the pharyngeal airway lumen did not change with increasing age. Reasonable data suggest that increasing airway length predisposes to collapse (140), as does increased tissue in the airway walls (parapharyngeal fat pads). In addition, White et al. (280) reported pharyngeal airflow resistance, measured during wakefulness, to increase with aging while Martin et al. (145) found airway pharyngeal luminal size, measured with acoustic reflection, to decrease with aging.

In subsequent studies conducted primarily during NREM sleep, Eikermann et al. reported that pharyngeal collapsibility (measured as the pressure necessary to close the airway), does increase with aging (Fig. 34), as does the increment in pharyngeal resistance occurring in the transition from wakefulness to NREM sleep (64). Fogel et al. found a similarly greater increase in airflow resistance at sleep onset (71). However, Thurnheer et al. (258) did not observe a greater percent increment in pharyngeal airflow resistance during sleep in older versus young subjects.

Several studies suggest that the neural control of the pharyngeal musculature may change with aging as well. Malhotra et al. reported a decrease in the response of the GG muscles to pulses of negative pressure measured during wakefulness (139). To the extent that this reflex allows the pharyngeal muscles to respond to threats to airway patency, a decrease in this reflex could render the airway more vulnerable. In addition, Worsnop et al. (288) and Fogel et al. (71) both reported greater decrements in upper airway muscle activation in the wakefulness to sleep transition in older versus younger normal subjects. Finally, Mortimore et al. (161) observed reduced tongue protrusion force with aging, but no difference in tongue fatigability in older versus younger patients/subjects.

Finally, there is little evidence to suggest that ventilatory control stability is adversely affected by aging. Increasing controller gain (generally the hypercapnic ventilator response) is most commonly the cause of ventilatory control instability and most evidence suggests that the hypercapnic response decreases with aging (188). In addition, sleep-wake changes in this response were similar when older versus younger subjects were compared (40). In addition, when total LG was actually measured during NREM sleep, it was consistently lower in older subjects when compared to younger ones (275).

One would have to conclude that aging may have important effects on upper airway anatomy/collapsibility and, potentially, pharyngeal dilator muscle function awake and asleep. These may contribute to the increasing prevalence of OSA in older individuals. However, ventilatory control stability does not appear to deteriorate with aging.

Apnea leading to more apnea

The previously described observation that apnea severity increases over time could be a product of aging or increasing obesity as described above. However, a third possibility is that the recurrent apneas/hypopneas themselves contribute to the progression of the disease. This discussion will be approached, as earlier, for obesity and aging.

There are two potential mechanisms by which apneas/hypopneas could affect upper airway anatomy/collapsibility. First, vibration (snoring) and high negative intraluminal pressures could easily traumatize the airway mucosa, leading to edema that would reduce the size of the airway. There are clearly data that suggest that there is airway edema present in apnea patients (6) and that this is reduced following CPAP use (207). How important this is in apnea pathophysiology or progression is unclear at this time. Second, the increased work of the pharyngeal dilator muscles during wakefulness and in restoring airway patency at the termination of apneas could lead to muscle hypertrophy. This could yield bulkier muscles that, again, could reduce the size of the pharyngeal airway. A number of studies do suggest that muscle hypertrophy can occur in the upper airway muscles of apnea patients (17,242), although not all studies support this conclusion (132). Again, the importance of such hypertrophy in apnea progression has never been quantified.

There are a number of ways that increased waking muscle activity (described earlier) and repetitive apnea during sleep could lead to less effective muscle performance. One way would be muscle injury. It has been hypothesized that the increased activity present in the GG muscle (and possibly other upper airway dilator muscles) during wakefulness and

the huge surges in muscle activity required to open the airway at the time of apnea termination could lead to both adaptive and/or maladaptive changes in the muscle (189). Some of this muscle activation could occur at a time of actual muscle lengthening (eccentric contraction) due to large negative pressures in the airway. Such eccentric contraction has been reported to cause damage in other muscles.

This has been studied in OSA patients by a number of investigators. Stauffer et al. originally reported a greater quantity of muscle and fat in the uvula of OSA patients compared to cadaveric controls (242). Woodson et al. (287), using similar tissue samples, reported extensive edema of the lamina propria, focal atrophy of muscle fibers, and disruption of muscle bundles in OSA patients, again compared to cadaveric controls (287). Edstrom et al. obtained tissue from the palatopharyngeus muscle of both OSA patients and normal controls and reported multiple abnormalities in the OSA group (62). These included atrophic fibers, some of which were angulated, abnormal fiber type distribution, and other morphologic abnormalities. Smirne et al. (235) compared tissue from the medium pharyngeal constrictor muscle of habitual snorers versus nonsnorers and reported increased Type IIa (fast twitch) and decreased Type I and IIb fibers in the habitual snorers. The Type IIa fibers in the snorers were also reported to be hypertrophied. Finally, Carrera et al. (41), studying the GG muscle, reported increased Type II fibers and fatigability in this muscle, with both abnormalities being reserved with CPAP. On the other hand, Series et al. (223), reporting on results from assessment of the musculus uvula, observed greater twitch and titanic tension in OSA patients compared to snorers. These values were similar when corrected for muscle fiber cross-sectional area, as the apnea patients had a larger cross-sectional area. He also found protein content and anaerobic enzyme activities to be greater in the apneic subjects. Finally, as reported by Smirne earlier (235), he observed more Type IIa muscle fibers.

Petrof et al. (190) obtained biopsies from the sternohyoid and geniohyoid muscles of the English bulldog, an animal with predominantly REM sleep apneas, and compared them to beagles without sleep apnea. He reported increased Type II fibers (as discussed earlier) and increased connective tissue in the bulldog sternohyoid muscle and more morphologically abnormal fibers (fissures or splitting of fibers, moth-eaten fibers) in both upper airway muscles of the bulldogs. He attributed these findings to muscle injury.

Despite these observations, most evidence to date suggests that the actual strength of the GG muscle is the same or greater in obstructive apnea patients compared to controls (33, 247). Thus, whether muscle injury is playing a role in the development or progression of sleep apnea remains unresolved. That being said, at least one study has reported considerable improvement in apnea severity following a period of upper airway muscle training. Whether this suggests a myopathy responsive to strength training is present in apnea patients or that simply increasing muscle strength leads to better performance in these dilator muscles is unclear at this time.

Another possible mechanism for apnea progression would be actual neural injury. Possible neural injury that could result from sleep apnea would likely fall into two general areas: afferent and efferent nerve damage. In terms of afferent pathways, it has been argued that snoring (vibration) and/or airway deformation might damage afferent nerves that could negatively impact reflex muscle control mechanisms important in the maintenance of airway patency awake and asleep. Larsson et al. (126) first assessed temperature sensation on the tongue and tonsillar pillars in a group of apnea patients compared to normal controls. He reported a reduced ability to detect changes in temperature in the apnea patients in both locations. Subsequently, Kimoff et al. (115) compared two-point discrimination and vibratory sensation on the soft palate, lip, and hand in three groups: sleep apnea patients, snorers, and normal controls. He found both sensory mechanisms on the soft palate to be reduced in both snorers and OSA patients compared to controls. OSA patients and snorers were not different. In the apnea patients, there was also an improvement in vibratory sensation after therapy with CPAP. Finally, Nguyen et al. (169) assessed sensation to air-pressure puffs in the velopharynx, hypopharynx, and larynx in OSA patients versus controls. At all sites except the hypopharynx, the pressure required to elicit sensation was greater in the apnea patients than the controls. The threshold to elicit the laryngeal adductor reflex was also elevated in the OSA patients. Thus, there is a reasonable literature suggesting pharyngeal sensory dysfunction in patients with OSA and probably snoring as well.

There are a number of papers that suggest there may be efferent nerve injury as well. Edstrom et al. first studied tissue samples from the palatopharyngeus muscle of OSA patients and controls and reported abnormalities of fiber size, type, and structure in the apnea patients, all of which "indicate a neurogenic origin" to the problem (62). Friberg et al. (72) and Lindman and Stal (132) reported similar findings in the same muscle. In both cases, a neurogenic problem, denervation, was implicated. However, as outlined above, Series et al. (223) found no such changes. More recently, Boyd et al. (37) assessed tissue from the tonsillar pillars and soft palate of apnea patients versus controls and reported a 5.7-fold increase in intramuscular nerve fibers and "direct evidence of denervation based on positive immunostaining of the muscle fiber sarcolemmal membrane for the neural adhesion molecule." Thus, there is reasonably strong evidence for some degree of muscle denervation in the OSA patients.

Whether the neural changes described above actually lead to muscle dysfunction, thereby contributing to apnea pathogenesis or progression, is unclear. Most evidence suggests that the upper airway muscles of the apnea patient have normal or greater strength than is encountered in controls (33, 247). On the other hand, Mortimore et al. (163) reported palatal muscle responses to pulses of airway negative pressure to be reduced in OSA patients during wakefulness when compared to controls. This difference disappeared over time with CPAP use. Alternatively, Berry et al. (29) reported similar reflex (in

response to negative pressure) control of the GG in apnea patients and controls. Thus, the clinical importance of the muscle/nerve damage described above is still questionable.

Finally, muscle fatigue could develop in apneic individuals with elevated muscle activation when awake and huge surges in pharyngeal dilator muscle activity when asleep. That the GG muscle can fatigue has been demonstrated in both normal humans (211) and animals. Additionally, short-term activation of the muscle in response to inspiratory resistive loading plus mild hypercapnia significantly reduced the endurance time of the muscle (211). In rats (73), hypoxia reduces endurance performance as well. Thus, the GG, a representative upper airway dilator muscle, like most skeletal muscle, will fatigue with continuous activation.

Whether patients with sleep apnea demonstrate greater fatigability than normal controls and whether a muscle endurance problem contributes to the pathogenesis of OSA is less clear. As outlined earlier, several studies have demonstrated a change in fiber-type distribution, with OSA patients and snorers both having more Type IIa fibers while normal controls have more Type I fibers (235). Carrera et al. (43) also reported greater fatigability in the GG muscle of the apnea patients that improved after treatment with CPAP (43). On the other hand, Blumen et al. (33) found similar endurance time and fatigability between OSA patients and controls. However, time to recovery of mean maximal force following a fatiguing event was consistently longer in the apnea patients than the controls (33). Thus, it remains unclear whether muscle fatigue plays a role in the pathophysiology of OSA.

There is also one paper that suggests that sleep deprivation, which can occur in patients with OSA, reduces genioglossal muscle activation during CO_2 rebreathing (130). This resolved when normal sleep duration was reestablished. Obviously, unresponsive dilator muscle could lead to progression of apnea severity.

In addition, as addressed earlier, there is an entire field of work studying memory in the respiratory control system with LTF being a prominent component of this memory with LTF being an increase in ventilation lasting up to several hours following exposure to intermittent hypoxia of relatively short duration (173). Most important to this discussion, animal and subsequent human studies indicate that such intermittent hypoxia can lead to increased upper airway muscle activation (particularly genioglossal) in a pattern similar to the increase in ventilation described previously (50,208). Thus, LTF could decrease apnea severity over time if there is a sustained increase in upper airway dilator muscle activity. However, there is no direct evidence that LTF is active in OSA patients or that it reduces the AHI in these patients.

Could recurrent apneas affect basic ventilatory control stability in a way that would lead to more frequent sleep disordered breathing events? Several studies suggest that sleep deprivation (potentially similar to the sleep fragmentation of OSA) leads to decreased hypoxic and hypercapnic ventilatory responsiveness (54,279), although not all studies support this concept (240). On the other hand, there are several reports indicating that patients with OSA have increased ventilatory responsiveness to hypoxia (98,166), with most believing this to be a result of intermittent hypoxia. In addition, a recent study suggests that untreated OSA may lead to an increase in the "dynamic response" of the ventilatory control system (the transient response to combined hypoxia and hypercapnia) (136). Whether these changes in chemoresponsivenss could affect LG and thereby apnea frequency is unclear at this time. It should also be noted that the LFT described earlier could have an inherent stabilizing effect on ventilator control due to the increased tonic drive to the respiratory system.

Finally, the arousal threshold to a respiratory stimulus may also be an important determinant of apnea severity as outlined above. Higher arousal thresholds should allow for recruitment of upper airway muscles and reestablishment of upper airway patency during stable sleep. A recent paper (136) suggests that untreated apnea leads to a substantially increased arousal threshold in some patients that would be expected to reduce apnea severity. Thus, some aspects of untreated OSA may actually improve respiratory stability during sleep.

In conclusion, it seems relatively clear that apnea severity can increase over time with and without weight gain. Whether this is simply due to the effects of aging on apnea pathophysiologic mechanisms or results from the direct effects of airway trauma and intermittent hypoxia remains to be resolved.

Conclusion

OSA is a disorder characterized by recurrent periods of upper airway partial or complete obstruction alternating with periods of hyperventilation, usually associated with arousal from sleep. It occurs in subjects whose passive pharynx is sufficiently narrowed so as to not permit passage of adequate airflow when dilator muscle activity decreases during sleep, unless compensatory mechanisms are engaged. Narrowing of the passive pharynx is related to a variety of bony and soft tissue abnormalities, with the extent of this narrowing being highly variable among patients with the disorder. Although some structural narrowing must be present for the disorder to occur, there is only a modest correlation between the severity of the structural changes and the severity of the clinical disorder, as measured by the AHI. This suggests that control mechanisms that determine the response to obstruction during sleep are important determinants of apnea severity. The disorder tends to progress with time. While an increase in body weight and age may be in part responsible, untreated OSA may itself lead to more OSA via structural changes in the pharynx or through changes in respiratory control.

The pharynx is endowed with a large number of muscles that can alter its dimensions and shape and many of these muscles respond to changes in chemical drive and pharyngeal negative pressure, two stimuli that increase over the course of obstructive events. A number of compensatory mechanisms to obstruction during sleep have been identified. These include an increase in inspiratory duty cycle (T_I/T_{TOT}) and

recruitment of pharyngeal dilator muscles secondary to the increase in chemical drive and the associated greater negativity of pharyngeal pressure. Although dilator muscle activity increases over the course of these events prior to arousal (indicating that reflex mechanisms can mount a response during sleep in OSA patients), it was strongly believed that only arousal from sleep can activate the dilators enough to open the airway. According to this interpretation, a patient with this disorder must have recurrent arousals, and therapy can be effective only through mechanical approaches that force open the airway. However, recent studies have clearly shown that in most patients reflex mechanisms related to the increase in chemical drive can open the airway without arousal. This has led to more detailed investigations of dilator muscle responses during sleep in OSA patients. These studies have identified several response characteristics. These include: (a) how much chemical drive must increase before the dilator muscles begin responding (dilator recruitment threshold), (b) how much dilator activity must increase before the airway will open (dilator opening threshold), (c) how much chemical drive must increase before dilator muscle activity reaches dilator opening threshold, (d) arousal threshold, (e) chemical control LG, (f) ability to increase T_I/T_{TOT}, and (g) gain of STP and possibly the LTF mechanisms. More importantly, it is now clear that the response characteristics that produce ventilatory instability vary considerably among patients and that the all-important dilator opening threshold is largely determined by unknown mechanisms that relate poorly to mechanical abnormalities. These new findings open the door to identifying nonmechanical approaches to influence the specific control mechanisms responsible for instability in individual patients. Currently, methods are being developed to identify the responsible mechanism(s) in individual patients (phenotyping), but much work remains to be done to determine how these characteristics can be altered to mitigate the instability.

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