Physiology in medicine: Obstructive sleep apnea pathogenesis and treatment—considerations beyond airway anatomy

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Obstructive sleep apnea (OSA) includes repetitive hypopneas, cyclical apneas, excessive hypoventilation, or a combination of these, induced via pharyngeal collapse to the point of ventilatory constraint (see Fig. 1A). Accordingly, the common clinical perspective is to view OSA as an exclusive problem of airway anatomy and to prescribe continuous positive airway pressure (CPAP) treatment. This approach has been highly successful in many patients. In this essay we review accumulating evidence in support of significant contributions to the pathogenesis of obstructive sleep apnea (OSA) from pathophysiological factors beyond the well-accepted importance of airway anatomy. Emphasis is placed on contributions from neurochemical control of central respiratory motor output through its effects on output stability, upper airway dilator muscle activation, and arousability. In turn, we consider the evidence demonstrating effective treatment of OSA via approaches that address each of these pathophysiologic risk factors. Finally, a case is made for combining treatments aimed at both anatomical and ventilatory control system deficiencies and for individualizing treatment to address a patient’s own specific risk factors.

Sleep-Induced Propensity for Cyclical Airway Obstruction

Two fundamental sleep-induced changes underlie OSA: 1) in marked changes in the passive mechanics of the upper airway, 2) in the critical reliance on chemosensitivity for control of respiratory motor output and its stability. First, the onset of the sleeping state results in a reduced tonic activation of upper airway dilator musculature leading to increased airway compliance and an enhanced collapsibility. This occurs in all humans. However, this sleep effect is especially problematic for a patient with OSA whose airway is narrower, longer, and more collapsible than that of someone without apnea, and who critically relies on compensatory activation of airway dilator muscles to maintain patency during wakefulness. The reduced lung volume in an obese recumbent patient during sleep also reduces caudal traction on the trachea, which adds significantly to the skeletal and soft tissue features promoting pharyngeal collapse (4, 76). Humans vary considerably in the pressure required inside the relaxed airway to close the passive upper airway (i.e., Perit1) during sleep; nonapneics require substantial negative suction pressures for closure, whereas most patients with OSA do not require generation of negative airway pressure to experience airway closure (32, 71).

Second, the loss of wakefulness removes an important vigilance component in the ventilatory control system, leaving the regulation of central respiratory motor output largely under chemoreceptor and mechanoreceptor feedback control. Non-rapid eye movement (NREM) sleep unmasks a highly sensitive, hypocapnic-induced apneic threshold. When PaCO2 is reduced below this threshold, central respi-

1 Perit defines the inherent mechanical properties of the upper airway and its surrounding tissue. It refers to the critical closing pressure of the airway as determined using a pressure-controlled system connected to a nasal mask that is capable of manipulating airway pressure in a step-wise fashion under passive conditions in the airway during sleep (i.e., without activation of airway muscle dilators).
Fig. 1. A: polysomnographic tracings of obstructive sleep apnea from a detailed experimental study of a patient with severe disease (apnea-hypopnea index = 56 events/h). Note the repeated oxygen desaturations as a result of severely impaired (hypopnea) or absent (apnea) airflow despite continual breathing efforts (Pepi) and the cyclical breathing pattern that ensues as the patient oscillates between sleep and arousal (downward pointing arrows). B: one obstructed apneic event (between the dotted vertical lines in A) to illustrate the compensatory events occurring during and following the obstruction. The cessation and resumption of flow defines the apneic event. Note the progressive increase in inspiratory effort (Pepi) and dilator muscle EMG (EMGgg) during the apnea, the transient arousal coincident with airway opening, and ventilatory overshoot at apnea termination. As the patient returns to sleep, note the gradual reduction in breathing frequency and flow rate, and increased pharyngeal pressure (signifying increased airway resistance) leading to the next obstruction. Evidence of snoring is shown on the flow tracing. Progressive increases in EMGgg activity occurred throughout the obstructive event, although in this instance they were not sufficient to restore flow, which occurred only upon arousal. Pharyngeal pressure serves as a measure of the inspiratory effort made against the obstructed airway, thereby reflecting the magnitude of central respiratory motor output in response to chemoreceptor stimuli accumulated during the obstructed apnea. Arousal threshold is determined by the pharyngeal pressure achieved through respiratory pump muscle contractions during an airway obstruction at the point of EEG arousal.

In summary, it appears that two fundamental effects of sleep are relevant to OSA pathogenesis; namely, increased airway collapsibility, and enhanced potential for ventilatory control system instability. Individual differences in ventilatory stability are dependent upon sleep state and the sensitivity with which the control system responds to transient disruptions in ventilation and chemoreceptor stimuli. We now consider evidence concerning how these influences might be linked to cause OSA in a sleeping human.

Links Between Central Respiratory Motor Output Instability and Cyclical Airway Obstruction

Several types of evidence implicate nonanatomical factors as important determinants of OSA. First, central respiratory motor output almost simultaneously engages both the phrenic motor neurons (serving chest wall pump muscles) and hypoglossal motor neurons (serving pharyngeal muscle dilators) (25, 28). CO₂-induced chemoreceptor drive elicits a linear recruitment of diaphragmatic electromyographic (EMG) activity as opposed to a nonlinear response of genioglossus airway dilator muscle EMG activity in animals and humans (25, 28, 41, 60). Second, the compliance and/or Pcrit of the passive upper airway [i.e., in an anesthetized, paralyzed (32), or sleeping human (15)] shows substantial overlap between patients with OSA and controls (32). Accordingly, correlational analysis shows that variations in passive Pcrit, by itself, account for only a very small portion of variations in the apnea-hypopnea index (AHI) (93).

Third, there is no precise boundary between central and obstructed apneas. For example, it has been known for some time that CPAP treatment or tracheostomy un masks an underlying ventilatory instability and periodicity in many patients with OSA (55, 79). Airway imaging studies during sleep also show substantial airway narrowing and even collapse to occur during hypocapnic-induced central apnea (see Fig. 2A), often producing cyclical, so-called mixed apneas (see Fig. 2B). Similarly, in selected patients with OSA and collapsible airways (Pcrit >0) combined with high chemosensitivity, cyclical obstructions were commonly preceded by transient ventilatory overshoots and hypocapnia (see Fig. 3A). When the transient hypocapnic periods were prevented and normocapnia was maintained (via selective small increases in FiCO₂ limited to the hyperpneic phase), most of the cyclical obstructions were also prevented (see Fig. 3B) (92). Conversely, if central ventilatory instabilities were superimposed (using brief hypoxic exposure) during sleep in snoring subjects with high upper airway resistance, complete airway obstructions occurred at the nadir of the oscillating drive to breathe (30, 83). Additional clinical examples of patients with OSA and mixtures of obstructive and central events include those living (57) or traveling to high altitudes (54) and those with collapsible airways who have developed heart disease or require narcotic medication (35).

OSA Pathogenesis

Two types of clinical observations underscore the importance of the interactions between airway anatomy and neu-
rochemical ventilatory control as determinants of OSA. On the one hand, although cyclical obstructions terminated by arousals are common, many patients with highly collapsible airways (positive Pcrit) maintain airway patency for significant periods of time during sleep without experiencing repeated cyclical obstructions or transient arousals (87, 93, 95). On the other hand, patients with mildly collapsible or even negative Pcrit but with high chemoreceptor gains experience periods of increased airway resistance and sometimes even airway closure with high AHI (13, 87, 93, 95).

We present two overlapping scenarios in Figure 4 for the pathogenesis of cyclical OSA, primarily on the basis of influences of airway collapsibility combined with neurochemical influences over pharyngeal dilators and respiratory pump musculature, and on sleep state stability. As outlined in Fig. 4, right, a patient with a highly collapsible airway (positive Pcrit) will often experience complete airway collapse when the compensatory tonic input to the upper airway is removed at sleep onset. In Fig. 4, left, a patient with a high chemosensitivity plus a mildly collapsible airway is likely to experience airway obstruction at the nadir of the oscillating central respiratory motor output. In either case, whether the obstruction is repeated and becomes cyclical will depend upon how the patient’s respiratory control system responds to the obstruction, as outlined in Fig. 4, bottom [also see the obstructed apnea and its aftermath in Fig. 2].

Fig. 2. Central apnea preceding obstructive apnea in subjects with a combination of unstable central respiratory motor output plus a collapsible airway. A: effects of a spontaneous central apnea on upper airway patency during non-rapid eye movement sleep. Fiber optic nasopharyngoscopy was used to determine airway dimensions at the level of the velopharynx or oropharynx. Initiation of central apnea is identified by the open inverted arrow, with the cessation of both airflow and oscillation of esophageal pressure (Peso). Complete airway occlusion occurred about 15–20 s following the onset of central apnea and before an inspiratory effort occurred, as noted by the constant Peso. Apnea continued and the airway remained closed for 35 s, showing partial return of airflow with resumption of inspiratory effort and then complete airway patency on arousal from sleep with accompanying ventilatory overshoot. [From Badr et al. (3).] B: cyclical, mixed (i.e., central followed by obstructed) apneas causing intermittent hypoxemia during non-rapid eye movement sleep. The cessation of airflow denotes the onset of apnea. The absence of cyclical changes in esophageal pressure over the initial 8 to 10 s of the apnea demonstrate that this initial phase of the apnea is due to the absence of central respiratory motor output and inspiratory muscle contractions. Over the latter half of the apnea, flow is still absent but progressive, cyclical increments occur in the negativity of esophageal pressure, indicating increasing inspiratory efforts against a closed airway in response to rising asphyxic chemoreceptor stimuli. The arrows shown at the termination of each apneic period indicate periods of transient cortical arousal accompanied by ventilatory overshoot. [From Dempsey et al. (11).]
The key ingredients to regaining respiratory stability are the ability to recruit airway muscle dilators and to effectively open the airway to restore air flow prior to arousal, because the transient arousal accentuates the ventilatory overshoot and hypocapnia, leading to subsequent hypopneas, apneas, and obstructions. Accordingly, how the chemoreceptor control system and the airway dilator musculature responds to accumulating CO2 and arterial HbO2 desaturation during the apnea, as well as the sensitivity of a patient’s arousal threshold, will determine whether initial obstructive events are followed by stable breathing, slow evolving hypopneas with occasional arousals, or repetitive obstructions (94).

A few recent reports each using substantial numbers of patients with OSA have documented that more than 80% of patients with moderate to severe OSA have a highly collapsible airway (passive Pcrit of 2 to 5 cmH2O), but 30–40% of these patients also have either high chemosensitivity, sensitive arousal thresholds, or sluggish responsiveness of upper airway dilators to chemical stimuli (15, 16, 87). These patients were all undergoing CPAP treatment, which after several months had been shown to reduce chemosensitivity (42, 80), widen the CO2 reserve below eupnea (65), increase arousal threshold (42), and improve the sensitivity of protective reflexes for upper airway patency in response to negative pressures (50). Studies in patients with newly diagnosed, untreated OSA revealed that more than half had enhanced chemoreceptor gain and narrowed CO2 reserve below eupnea, and almost all patients had a Pcrit in the −2 to +6 cmH2O range (92).

In summary, accumulating evidence points to several links between the regulation of central respiratory motor output and pharyngeal patency. For example, increasing or decreasing central instability in many patients with inherently collapsible airways will, respectively, exacerbate or reduce airway obstructions. Finally, whether an airway obstruction precipitates further cyclical obstructions critically depends on how airway dilator muscles, respiratory pump muscles, and sleep state respond to the apneic-induced accumulation of chemoreceptor stimuli. Finally, recent surveys reveal that nonanatomical risk factors for cyclic obstruction, including high loop gain, sensitive arousability, and nonresponsive airway dilator musculature are present in significant numbers of patients with OSA. These findings have implications for alternative, individualized treatments for OSA.

Assessment of Nonanatomical Risk Factors

Characterization of nonanatomical risk factors for OSA in individual patients has included several different approaches in recent years. For loop gain assessment, approaches have included 1) CPAP manipulation to determine the ratio of ventilatory decline (achieved via reduced CPAP pressure) to ventilatory response (achieved upon abrupt restoration of pressure to the point of airway patency) (85); 2) the ventilatory response to exogenous inspired CO2 in wakefulness using a pseudorandom binary CO2 delivery method (20); or 3) progressive increases in tidal volume via assisted mechanical ventilation during sleep to determine the hypocapnic-induced apneic

Fig. 3. A: polysomnographic recording from a patient with severe OSA [apnea-hypopnea index (AHI) ~60/h] during air breathing. Cyclical obstructive apneas were indicated by the absence of flow despite continued respiratory efforts and the paradoxical motions of rib cage and abdomen. B: most of the obstructed apneas were prevented in this patient when a selective rebreathe mask-reservoir system was used to raise FICO2 only during the hyperpneic phase of an event, thereby preventing the transient hypocapnia and holding PETCO2 at levels experienced equal to those during stable eupneic air breathing (not shown). The 4-min periods shown for both control (A) and isocapnic treatment (B) conditions were representative of the breathing pattern, PETCO2, and AHI experienced during the total 90- to 95-min periods of control and treatment conditions studied in this patient. A reduction in AHI of 30 to 90% with this isocapnic treatment was observed in 14 of 26 patients with moderate to severe OSA and Pcrit of ~2 to +5 cmH2O. AB, abdominal movement; RC, rib cage movement. [From Xie et al. (92).]
Pathogenesis of Cyclical OSA

Anatomical Predisposition To Airway Closure

Sleep

High Loop Gain + Mildly Collapsible Airway

Withdrawal of Wakefulness Drive to Breathe, ↑ Dependence on ↑PaCO₂

Unstable Resp. Motor Output to Airway + Pump Muscles

Obstructed Apnea

↑ Chemo Stimuli Recruit Airway Dilators + Pump + Higher CNS

Arousal + Airway Open = Ventilatory Overshoot

Pump and Airway Dilator Muscles Inhibition via Hypocapnia + Lung Stretch + Sleep Resumption

Highly Collapsible Airway (Pcrit > 0)

Withdrawal of Neuromuscular Compensation to Upper Airway Dilator Muscle + ↓ FRC + Airway Edema

↑ UAW Compliance / Collapsibility

Threshold, thereby allowing calculation of chemosensitivity to CO₂ below eupnea, plant gain, and the CO₂ reserve (ΔPETCO₂ between eupnea and the apneic threshold) (90). These methods are time consuming and are primarily research tools. There may also be strong indicators of important apnea-causing characteristics contained in a patient’s routine polysomnograms, such as the occurrence of multiple central or mixed apneas, or repetitive cycles of periodic breathing with similar durations (see Fig. 2B), as markers of high loop gain. Also, the occurrence of only minor O₂ desaturations preceding transient arousals may signify a sensitive arousal threshold. The unmasking of cyclical central apneas or hypopneas during the CPAP trial is also a significant indicator of a high gain, unstable control system (79). Mathematical models to predict loop gain on the basis of a patient’s spontaneous periodic pattern as measured in a routine polysomnogram have been proposed (46, 67), but to date these have had significant limitations, such as the need for strict sinusoidal periodic patterns of breathing, which are prevalent in conditions such as heart failure but rare in OSA.

Recently, Wellman et al. (86) proposed the manipulation of CPAP pressures to determine loop gain, arousal threshold, and response of the upper airway dilators to increased ventilatory drive, all achieved noninvasively within a single night of study requiring only the standard equipment used for routine polysomnograms. Some type of combination of the latter approach using CPAP manipulation with mathematical modeling may eventually provide a usable clinical tool for patient characterization for purposes of individualizing treatment (see Treatment Implications).

Treatment Implications

Given that several nonanatomical determinants of cyclical airway obstruction are prevalent in many patients with OSA, that appropriate CPAP therapy is not acceptable to about one-half of patients diagnosed with OSA, and that oral appliances and surgical therapies are not always effective, alternative therapies or combinations of therapies are needed and preferably tailored to the specific risk factors of a patient. Most recently, three types of nonanatomical treatments have been attempted in fairly sizable groups of patients with moderate to severe OSA. These therapies include reducing loop gain to stabilize central respiratory motor output, raising the arousal threshold, and recruiting airway dilator muscle tone.

Reducing chemoreflex/plant gain effects on both central and obstructive events. The carbonic anhydrase inhibitor acetazolamide stimulates ventilation via a mild systemic metabolic acidosis, thereby reducing plant gain with little or no increase in CO₂ chemosensitivity. As might be expected, this treatment was highly effective in reducing most central apneas and periodicities in patients with heart failure and Cheyne-Stokes respiration (33) and in normal subjects at high altitude (75). Even with mild to severe OSA, 1 wk of acetazolamide treatment reduced AHI by more than one-third in about half of a group of 13 patients, and this effect was attributable solely to a reduced plant gain (achieved via the accompanying steady state hyperventilation and reduced PaCO₂) with no effect on chemoreflex gain, pharyngeal collapsibility (Pcrit), or arousal threshold (16). Administering oxygen (via nasal cannula) sufficient to maintain HbO₂ saturation in the 95–98% range will reduce chemosensitivity to CO₂, widen the CO₂ reserve between eupnea and the apneic threshold (51, 91), and reduce AHI in many patients with chronic heart failure and Cheyne-Stokes type periodic breathing and central apneas (19, 23, 34, 44). Hyperoxia was also effective in significantly decreasing AHI in a minority of patients with OSA, especially those with already elevated chemoreceptor gain (88, 92). On the other hand, prolonged apnea lengths and some cases of increased obstructive events have also been reported with the use of hyperoxia (19, 29, 88).

3 Patients with chronic heart failure and periodic breathing during NREM sleep have been shown to have high chemosensitivity, reduced CO₂ reserve, increased circulation time, impaired cerebrovascular reactivity (to CO₂), increased pulmonary vascular pressure, or a combination of these, all of which will contribute to unstable respiratory control (35).
Intermittent hypoxemia, similar to that attending OSA, enhances carotid chemoreceptor sensitivity through increased expression of angiotensin II type I receptors, and increased oxidative stress and inflammation. Accordingly, drugs that block these processes, such as losartan or those with anti-inflammatory properties will prevent carotid body sensitization (47, 56, 58, 59, 61). Although these pharmacologic-induced reductions in CB gain have not yet been tested, they may be useful in stabilizing central respiratory motor output and reducing cyclical airway obstructions in OSA. Also, clonidine, an α2-adrenergic agonist, was recently reported to reduce the slope of the CO2 response below eupnea during NREM, thereby widening the CO2 reserve in healthy nonapneic subjects (68).

Raising arousal threshold. The rationale for using sedation as therapy for cyclical OSA is to help maintain sleep state sufficiently long during an airway obstruction to allow chemoreceptor stimuli to reach sufficiently high levels to activate airway dilator muscles and open the airway to restore flow prior to arousal. This would depress transient arousals and their accompanying ventilatory overshoots that lead to cyclical obstructive apneas (14). This goal of increasing arousal threshold could also be realized if sedation caused a significant shift in NREM sleep from lighter to deeper sleep stages, during which the arousal threshold is significantly increased. On the other hand, sedative use must avoid an excessive prolongation of apnea duration or an impairment of dilator muscle recruitment, leading to severe intermittent hypcapnia and hypoxemia (66). Indeed, sedative agents such as alcohol and some benzodiazepines (38, 40) will also impair dilator muscle recruitment. Furthermore, any sedative use should be avoided in patents with OSA and daytime CO2 retention. To date, in unselected populations of patients with OSA, sedative medications have produced mixed AHI results (5, 7, 26, 38, 40, 43, 45, 62, 63, 72, 82). More promising are recent findings in patients with OSA selected for a very low (i.e., sensitive) arousal threshold in whom AHI was reduced by 40–50% with significant shifts from stage 1 to stage 2 sleep state and improved sleep quality (14).

Recruitment of upper airway dilators. Substantial progress has been made in our understanding of the basic neurobiology of upper airway regulation and specifically the critical role in sleep-induced muscle atonia played by serotonergic and noradrenergic inputs (11, 18, 22, 27, 39, 74). Unfortunately, this progress has not yet been translated into successful pharmacotherapeutic trials because drugs with either serotonergic or noradrenergic effects have proven universally ineffective (6, 24, 37, 64, 69, 81). To date these trials have been statistically underpowered and no attempt has yet been made (as with studies on sedatives or loop gain modifiers summarized above) to identify subsets of patients who might respond. Recently, a potassium channel blocking compound has elicited major reductions in upper airway collapsibility in an anesthetized pig model (89), but this has not yet been tested in the sleeping state, either in animals or humans. Intermittent electrical stimulation of the hypoglossal nerve synchronized to inspiration using chronically implanted electrodes has recently been shown to be effective in reducing OSA and was relatively well tolerated by patients (12).

Another approach is to consider a ventilatory stimulus with the capability for also effectively recruiting upper airway dilator muscles. The effect of acetazolamide in reducing AHI in some patients with OSA may be attributed in part to upper airway dilator muscle recruitment in addition to its effect on stabilizing central respiratory motor output by reducing plant gain (16). Even more effective is the mild hypercapnia achieved via increased FiCO2, which was shown to remove flow limitation in snorers (2) and even to prevent most cyclical obstructed apneas in 17 of 21 patients with OSA without disrupting their sleep state (92) (see Fig. 5). These AHI-lowering effects of mild hypercapnia occurred in patients with OSA with a wide range of chemosensitivity and CO2 reserve, and with highly collapsible airways (Pcrit −2 to +5 cmH2O). Presumably, the 2 to 5 mmHg increases in PETCO2 achieved with continuous deadspace rebreathing resulting in an approximately 30–40% increase in V̇E above stable air breathing control values was sufficient to both stabilize central respiratory motor output and effectively recruit upper airway muscle.
dilators and prevent cyclical airway obstructions. This range of hypercapnia and increased ventilatory drive approximates that estimated by Younes to be sufficient to effectively open the airway in patients with OSA during an obstructive apnea without requiring electroencephalographic arousal (94). The downside of this hypercapnic therapy is the potential side effects on sleep state stability and sympathetic activation due to any inadvertent excessive increases in P_{ACO2}, and the challenge of delivering and monitoring CO_{2} in a controlled fashion outside of a laboratory setting. Alternatively, a pharmacological approach, as yet undiscovered that might mimic these beneficial effects of 1–3 mmHg hypercapnia on effectively recruiting respiratory motor output to both upper airway and pump muscles without increasing chemosensitivity or arousability, might offer a reasonable approach in most patients with OSA.

Combined treatments. Combining treatments has been shown to be effective for some types of central sleep apnea, especially for residual central instabilities uncovered by CPAP therapy (9, 21, 77, 78). This approach may also be effective in OSA. So, for example, use of hyperoxia or acetazolamide to reduce chemoreflex and plant gain, respectively, may be relatively well tolerated therapies whose effectiveness in OSA would be markedly enhanced if Pcrit could also be just partially reduced. In turn, these moderate reductions in airway collapsibility could be obtained with even small reductions in body weight (70) or with mandibular advancement (53), or by adjustments in body position to avoid supine sleep or neck flexion. Thus, although none of the nonanatomical approaches by themselves might be universally effective in treating patients with moderate to severe OSA, they may be sufficiently complementary to alternative means of reducing the anatomical component and be more acceptable to a CPAP-intolerant patient.

Approaches in addition to CPAP to treat OSA have targeted three physiologic causes: 1) reducing gains to stabilize respiratory motor output, 2) using sedatives to reduce heightened arousability, and 3) reducing airway collapsibility via recruiting upper airway muscle dilators. To date these approaches have produced mixed results, with the most consistent success achieved when the treatment was tailored to an individual patient's specific deficiency, such as a high chemosensitivity or a low arousal threshold.

Summary
We have considered available evidence that implicates significant contributions from neurochemical control of central respiratory motor output to cyclical OSA through its effects on output stability, upper airway dilator muscle activation, and arousability. Using specific therapies to address these nonanatomical contributors to OSA has been shown to be effective in significant numbers of patients with OSA and with high controller and/or plant gains. Limited success has also been met with the use of sedatives to reduce arousability, at least in patients with already sensitive arousal thresholds. A challenge in using these approaches for treatment purposes is to simplify our ability to recognize the specific risk factors in the OSA population so that therapy can be individualized. We also need to continue to explore new agents for reducing loop gain and arousability and especially for effective stimulation of upper airway muscle dilators without invoking confounding side effects on chemoreceptor gain or sleep state continuity, or excessive sympathetic activation. Given the significant amount of information available on these problems, the onus is also on sleep practitioners and especially those leaders in the field charged with formulating treatment guidelines (49) to seriously consider the role of alternative therapies tailored to a patient’s individual relevant characteristics, when encountering a patient with OSA who is intolerant of CPAP.

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