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Fifty Years of Physiology in Obstructive Sleep Apnea

Before 1978, investigations focused on the obesity–hypoventilation syndrome, consisting of anecdotal reports of airway obstruction, with the most significant being a report by Gastaut and coworkers (1) that described episodes of obstruction *in one patient*. Dramatic improvement after tracheostomy confirmed that obstruction was in the upper airway.

In 1978, Remmers and colleagues (2) published their landmark study about mechanisms of obstructive sleep apnea (OSA). Key observations were that the airway remained closed/narrowed even though tongue activity was increasing and that the airway opened with a disproportionate surge in tongue activity associated with arousal. This, along with concurrent increase in negative pharyngeal pressure, led them to propose the "balance of forces" theory; when the airway obstructs (i.e., narrows enough to impede normal flow demand), asphyxia develops and tongue activity increases, tending to pull the tongue forward, but, because of concurrent diaphragm activation, the negative pressure behind the tongue also increases, countering the forward tongue movement. This continues until there is arousal-mediated recruitment of the airway dilator muscles.

The implications of this study were huge because these findings meant that:

1. Until we can make genioglossus activity increase more than the diaphragm's, we have only one alternative for therapy: keep the airway open by physical means. For the next 25 years, investigations into therapy focused almost exclusively on physical means to widen the pharynx (continuous positive airway pressure [CPAP] (3), surgery, and mandibular advancement devices).
2. Arousal is the essential mechanism for opening the airway.

After this publication, physiology research focused on why the pharynx is narrowed, circumstances of activation of pharyngeal muscles, and mechanism of arousals.

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Why Is the Pharynx Narrowed?

A variety of imaging, acoustic, manometric, and endoscopic techniques were directed at determining what underlies pharyngeal susceptibility to collapse. Among the numerous investigators in this area, Richard Schwab (imaging), John Remmers (passive mechanical properties), and the Hopkins group (Schwartz, Smith, and Permutt) deserve special mention. Among the important findings from these studies:

1. The pharynx is narrower and more collapsible in patients with OSA. As opposed to active constriction, anatomically narrowed upper airway is the root cause of OSA. Hence, pharyngeal dilators must be activated to obtain adequate airflow during sleep.
2. The relation between pharyngeal pressure and maximum flow is linear. Accordingly, pharyngeal mechanical properties can be described by the slope and intercept (pressure at which flow is zero; Pcrit) of the relation between CPAP pressure and flow within the flow-limited range. Furthermore, Pcrit determined immediately after reduction of CPAP reflects collapsibility of the passive pharynx, whereas Pcrit determined after sustained reductions of CPAP reflects collapsibility after compensatory mechanisms were engaged. These important findings (Hopkins group) made it possible to evaluate passive pharyngeal mechanics and effectiveness of compensatory mechanisms through simple procedures that can be implemented clinically.
3. It became clear that, although a narrowed airway is necessary for OSA to develop, severity of OSA (apnea–hypopnea index) is only weakly related to Pcrit. This highlighted the importance of control mechanisms (response to the obstruction) in determining OSA severity.

Unfortunately, despite numerous attempts, no particular anatomic feature(s) could predict with accuracy who has OSA or who will respond to a particular surgical intervention.

Circumstances of Activation of Pharyngeal Muscles

Hundreds of studies were devoted to this topic using conscious, anesthetized, and sleeping animals and conscious and sleeping

normal subjects and patients with OSA. The action of each pharyngeal muscle was described. Pharyngeal muscles were shown to respond to chemical stimuli and negative pharyngeal pressure in anesthetized and sleeping animals, whereas in humans, negative pharyngeal pressure appeared to be the main stimulus. Pharyngeal mechanoreceptors were shown to be the mediators of the reflex. The findings of these studies are summarized in a recent review (4). David White and his collaborators deserve much credit for this work.

This topic cannot be left without mentioning a 1987 study on sleeping cats by Haxhiu and colleagues (5) that, in retrospect, described a fundamental problem in OSA: the genioglossus does not begin responding to chemical drive in earnest until chemical drive has increased a threshold amount.

Mechanism of Respiratory Arousals

Gleeson and colleagues (6) were the first to show that arousals occurred when a certain negative pharyngeal pressure was reached, regardless of mechanism. The negative pharyngeal pressure reached immediately before arousal in patients with OSA became the standard metric for measuring respiratory arousal threshold. Arousal threshold ranged widely among patients with OSA. Another fundamental observation was that arousal threshold is not constant but changes continuously throughout the night (7). Richard Berry (8) and David White and colleagues from Harvard (4) deserve much credit for these advances. An important outcome of this research is that negative pharyngeal pressure became recognized as a common stimulus both for recruitment of pharyngeal dilators and for arousal.

Failure of this extensive research to yield new therapeutic approaches led to increasing difficulty of obtaining funding for physiological research in OSA. At the beginning of this century, it appeared that dependence on little-tolerated devices was unavoidable. However, an inquiry into a long-recognized simple observation promised to offer alternate approaches to therapy: patients with OSA often have periods of stable breathing in the same position/sleep stage associated with repetitive events at other times (9). These stable periods could not be explained by spontaneous changes in airway mechanical properties, as might occur with isolated head movement (9). Furthermore, periods of stable breathing are associated with greater pharyngeal dilator activity (10), whereas the opposite would be expected if stability resulted from better airway mechanics. These observations led to the conclusion that under appropriate conditions, dilators can open the airway without arousal, and, by extension, whether the patient develops recurrent cycling or stable breathing is determined by how stable respiratory control is.

As taught by Michael Khoo and colleagues in relation to periodic breathing (11), factors that determine instability after a hypopnea are delay before a ventilatory response can be initiated, how much blood gas tensions deteriorate during this delay (plant gain [G_P]), and how much ventilation increases in response to these gas changes (controller gain [G_C]). Ventilatory response/initial perturbation is loop gain (LG), given by $G_P \times G_C$ (11). If LG is greater than 1, the response overcorrects gas tensions, another hypopnea/apnea occurs, and the cycle repeats.

Before addressing the research done to investigate instability in OSA, I must point out some important differences between OSA and the periodic breathing analyzed by Khoo and colleagues:

1. With an unobstructed airway, delay is determined by lung–carotid circulation time (~10 s). In OSA, ventilatory response cannot be initiated until pharyngeal dilators are activated enough to open the airway. Thus, respiratory drive at event termination (terminal drive) is determined by the drive (i.e., negative pharyngeal pressure) required to sufficiently activate the dilators, regardless of circulation delay, G_P, or G_C. These latter characteristics simply determine the time to reach this level of activation (event duration).
2. Progressive asphyxia results in progressively more negative pharyngeal pressure (8). Required dilator activation, and hence terminal drive, is reached either through chemically induced increase in pharyngeal negative pressure or via arousal, as determined by the lower of (*a*) drive required to sufficiently activate the dilators without arousal (effective recruitment threshold [12]) and (*b*) drive that results in arousal (arousal threshold). These two variables, not G_P or G_C, are the main determinants of instability in OSA. If both are high, terminal drive will be high, promoting instability.
3. Terminal drive reflects the pulmonary gas tensions that existed a circulation time (~10 s) ago. Accordingly, drive continues to increase beyond airway opening. This increase is related to how much pulmonary gas tensions worsened in the terminal portion of the event, a function of conventional G_P, and the response to these changes, a function of G_C. Thus, conventional stability variables continue to play a role, but it is limited to the increase in ventilation beyond the first open breath.
4. With OSA, postevent mechanical impedance is not necessarily normal; many/most patients snore and have flow limitation during the open phase. How much the airway opens after events is thus an important determinant of overall LG.

It is clear that factors that determine instability in OSA are more complicated than in central instability. Factors that need to be considered include effective recruitment threshold, arousal threshold, and response of upper airway resistance to increasing chemical drive.

The first attempt at measuring some of these variables was reported in 2007 (12). Pcrit, circulation delay, effective recruitment threshold, arousal threshold, and ventilatory response to an asphyxic challenge (a measure of G_C) were measured in 21 patients with OSA while on CPAP. Another study determined the response of genioglossus to increasing chemical drive (13). The results of these studies revealed that:

1. Pcrit ranged from -2 to 10 cm H_2O (12).
2. Circulation delay was normal (12).
3. Effective recruitment threshold ranged 20% to >300% of eupneic drive (12). In two-thirds of patients, it was <100% eupneic drive.
4. Range of arousal threshold was equally wide. In two-thirds of patients, it was <120% eupneic drive (12).
5. Five-breath response to asphyxia ranged from 50 to 450% of eupneic V_E. Importantly, the increase in drive required to reach effective recruitment threshold or arousal threshold in two-thirds of patients was achieved with fairly trivial changes

in gas tensions (~3 mm Hg increase in end-tidal carbon dioxide pressure and ~4% decrease in oxygen saturation as measured by pulse oximetry) (12).
6. As described by Haxhiu and colleagues (5), genioglossus showed little response to increasing chemical drive up to a threshold (13). This threshold ranged up to 400% of eupneic ventilation.

Most importantly, there was little correlation between these different variables, indicating that the mechanism of instability varies greatly among patients. Because many of these variables can be manipulated pharmacologically, these findings suggested a potential for using pharmacological means that target the offending mechanism(s) in each individual.

Phenotyping patients with OSA and individualized therapy was subsequently adopted by several investigators, most notably Andrew Wellman and associates. So far, the results have been disappointing. Interventions based on phenotyping rarely reduced OSA severity to an acceptable level, and in the few individuals in whom this happened, it was difficult to rule out the effect of night-to-night variability in OSA severity. No patient, to my knowledge, has been maintained in the long term on a therapy that was identified through phenotyping despite efforts spanning nearly a decade. Several reasons contribute to this unfortunate outcome:

1. Determining phenotype from routine polysomnography data is difficult, if not impossible. Complex interventions are needed, and this is not practical. Among the difficulties are (*a*) Upper airway resistance during the open phase cannot be assumed to be normal (*see* #4 in the first list in this section). (*b*) The contribution of the usually-present cortical arousal to postevent ventilation cannot be ignored or assumed to be constant. Given these two considerations, it is not possible to determine the increase in respiratory drive during the event from postevent ventilation, and by extension, calculation of LG, arousal threshold, and the increase in drive required to reflexly open the airway becomes problematic. (*c*) Measuring true inspiratory flow without a full face mask and proper flow sensors is problematic given that many patients open their mouth at the end of events.
2. The change in arousal threshold by currently available hypnotics is too small relative to what is required to bring it to a higher level than effective recruitment threshold (14). Furthermore, the effect of hypnotics wanes as night progresses. Accordingly, even if successful in aborting events, they would be effective for only a part of the night.
3. When arousal threshold is low, which is when hypnotics may be indicated, effective recruitment threshold cannot be determined. If the unknown effective recruitment threshold is much higher than arousal threshold, hypnotics will simply delay arousal, not prevent it, thereby aggravating hypoxemia. Given that hypnotics increase arousal threshold only slightly, they would be effective only in patients in whom both arousal and effective recruitment thresholds are low. The frequency of this combination is unknown, but limited observations suggest that it may be uncommon (12).
4. Whereas oxygen breathing is effective in lowering LG in central apneas, its effect in OSA is limited to blunting the additional increase in ventilation beyond airway opening (*see* #3 in the first list in this section).
5. Reducing effective recruitment threshold is quite difficult by pharmacological means. One approach would be to raise baseline respiratory drive such that the dilators are primed to respond. Respiratory stimulants such as acetazolamide proved ineffective before, almost certainly because the increase in baseline ventilation (<30%) is too small relative to what is needed (*see* #3 in the second list in this section). Higher levels of drive can be achieved by breathing CO_2. However, sleep quality at the required levels of stimulation becomes very poor (my unpublished observations).

In summary, although our understanding of OSA pathogenesis has improved considerably, physiology has still failed to provide alternative therapies. However, at least we now know the fundamental problems that underlie OSA. These are:

1. The pharynx is sufficiently collapsible to preclude adequate flow without pharyngeal dilator activation.
2. Respiratory drive must increase above eupnea before the dilators begin responding in earnest. Although, in most patients, the required increase can be achieved with minor, acceptable changes in gas tensions, this is precluded by problem 3.
3. There is exquisite sensitivity of arousal mechanisms to small changes in respiratory drive.

Where Do We Go from Here?

With respect to the first problem, further investigation of the anatomy and mechanical properties of the pharynx may lead to better/more reliable surgical approaches.

To address the second problem, we need to increase dilator activity, without increasing respiratory drive, which disrupts sleep. Direct hypoglossal nerve stimulation appears promising in selected patients (15). Selective stimulation of the hypoglossal nucleus in the brainstem is another promising approach (16). A recent study found that tonic genioglossus activity remains elevated after obstructive events for up to a minute despite return of chemical drive to, or below, baseline (afterdischarge) (17). This offers protection against reobstruction. Magnitude and duration of afterdischarge vary considerably among patients with OSA (17). Drugs that promote the afterdischarge may offer protection.

With respect to the third problem, measures that more effectively increase arousal threshold without excessive sedation are likely to benefit all but patients with high effective recruitment threshold (e.g., >100% eupneic drive). Promoting deep sleep through drugs that increase delta activity is an active area in insomnia research (18), which may lead to benefits for OSA therapy as well. Finally, a recent study found that the rate of sleep recovery after arousals varies considerably among patients (19). Those in whom sleep recovery is slow remain vulnerable to repeat arousals for several minutes after each arousal. Agents that influence the speed of postarousal sleep recovery may be effective in stopping the cycling. ■

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