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Evidence-Based Treatment for Sleep-Related Breathing Disorders

Identification of nonanatomic factors facilitates trait-targeted therapy

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ABSTRACT

Although some level of anatomic impairment is present in all patients with SRBDs, variable responses to anatomic-directed therapies have revealed that other nonanatomic variables play important roles in the development of these conditions. These physiologic factors, which include compensatory neuromuscular responses, such as low arousal threshold, high loop gain, and poor muscle recruitment, can be identified using data from standard sleep studies and leveraged to direct trait-targeted therapies. This article discusses how patients' physiologic traits interact with anatomic factors to create disease states that differ in their underlying pathophysiology, examines some of these physiologic traits and their specific effects on ventilation, and presents trait-targeted therapeutic options that clinicians can use to individualize treatment and optimize airway and sleep outcomes.

Sleep-related breathing disorders (SRBDs), including obstructive sleep apnea (OSA) and upper airway resistance syndrome (UARS), are characterized by decreased pressure that results in recurrent partial to complete collapse of the pharyngeal airway during sleep and are increasingly being recognized as a major public health problem because they affect at least one-third of the adult population.[1,2] Although SRBDs are medical conditions, dentistry is uniquely positioned to screen, treat, and even prevent these chronic diseases with oral appliances, orthodontic treatment, and oral surgical procedures. In fact, in 2018, the American Dental Association adopted a policy statement mandating that dentists provide screening and treatment for SRBDs among children and adults.[3]

Historically, treatment has been determined by a diagnosis that is based on the number of airway events that occur during an hour of sleep. However, there is growing interest in determining which mechanisms represent the root causes of these airway challenges. Patients with similar disease severity index scores (ie, apnea-hypopnea index [AHI]) may have entirely different causes and therefore, could benefit from customized therapies that target the specific causal "traits." The variability among patient responses to anatomic-directed therapies is evidence that we need to do more. Appreciating this heterogeneity of the causes and consequences of SRBDs, it is no longer desirable or appropriate to treat based on disease severity index scores alone.

Pharyngeal anatomic impairment in patients with SRBDs can be modest, and because as many as 50% of OSA patients are non-obese, approximately 20% of patients with SRBDs have a level of upper airway impairment that is no different than that of people without SRBDs.[4] Thus, for many patients, nonanatomic factors, or "traits," that modulate pharyngeal patency are crucial determinants in the development of an SRBD.[5] In fact, recognizing that SRBDs are caused by the interplay between a variety of physiologic (ie, nonanatomic) variables and anatomic pharyngeal collapsibility, it can be appreciated that the diagnosis, management, and treatment of SRBDs requires a deeper understanding of the pathophysiology of the underlying disease (Figure 1).

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LEARNING OBJECTIVES

- Explain the relationship between anatomic and physiologic factors in the development and evidence-based treatment of SRBDs.
- Define pharyngeal critical closing pressure and arousal threshold.
- Describe how the disproportionately large ventilatory response associated with high loop gain will result in a greater degree of hypocapnia and a subsequent reduction in ventilatory drive.
- Summarize how poor upper airway muscle recruitment interacts with the arousal threshold and loop gain to contribute to repetitive apnea.

Disclosures: The author had no disclosures to report.

Dentists have been anatomically phenotyping patients by identifying structural deficiencies associated with sleep-related breathing disorders, such as high body mass index, retrognathic mandible, maxillary hypoplasia, high-arched palate, obstructed nasal passageways, tongue position, hyoid bone level, and various cephalometric and cone-beam computed tomography data points.[6] Beyond anatomic variables, which are the biggest causal factors of SRBDs, the literature reveals that approximately 69% of affected patients have at least one nonanatomic trait that contributes a variable influence to their airway function.[5,7] These physiologic traits include compensatory neuromuscular responses, such as arousal threshold, loop gain, and muscle recruitment. The nonanatomic contributors become less significant as the anatomy becomes more deficient and more significant as the anatomy becomes closer to normalized.

Previously available treatments only targeted a single trait; however, data quantifying these airway challenges can now be extracted from standard overnight sleep studies, which helps clinicians efficiently select between appropriate therapies to arrive at the most successful treatment. A clear understanding of each of the trait targets, how the data is collected, and which treatments show promise is the basis of precision treatment.

Pharyngeal Critical Closing Pressure

Pharyngeal collapsibility refers to how likely the pharynx is to collapse at a given pressure. The gold standard measurement of pharyngeal collapsibility is called the pharyngeal critical closing pressure (Pcrit), which is measured in cm H_2O (Figure 2). Pcrit is an objective measurement of upper airway collapsibility—an important pathogenetic factor in OSA. It is desirable to have a Pcrit that is very low (ie, a negative number). When a patient's Pcrit is "reduced" or "lowered," it means that it has become a negative number of greater magnitude, and therefore, a larger pressure drop is required to collapse the airway. The higher the Pcrit value (ie, a negative number with lesser magnitude or a positive number), the more easily the pharynx will collapse. The lower the Pcrit value, the better.

When atmospheric pressure is 0 cm H_2O, a normal, healthy airway can withstand a pressure of -8 to -10 cm H_2O before it collapses. It is normal to have pharyngeal pressure drop during inspiration. If a person's Pcrit increases above -8 cm H_2O (ie, to a negative number of lesser magnitude or a positive number) and airway pressures fall below Pcrit during inspiration (ie, typically -8 to -10 cm H_2O), the airway can collapse.[8,9,10]

Apneic patients tend to have a Pcrit above 0 cm H_2O, and patients who predominantly experience hypopneas usually have a Pcrit of 0 to -4 cm H_2O. Generally, individuals who snore will have a Pcrit of -4 to -6 cm H_2O, whereas UARS patients have a Pcrit of -2 to -6 cm H_2O.[8,9,10,11]

Effective therapy requires a lowering of the patient's Pcrit to below whatever the airway pressure maximally drops to during inspiration. Therefore, clinicians need to quantify the baseline Pcrit in order to make rational treatment choices. A Pcrit above -5 cm H_2O reflects anatomic compromise. Anatomic-directed therapies, including surgical intervention, continuous positive airway pressure (CPAP) therapy, oral appliance therapy, weight loss, and positional therapy all have an impact on a patient's Pcrit value. Selecting and combining therapeutic choices that lower the Pcrit to at least -8 to -10 cm H_2O will maintain a patent airway.[5,8]

Changing from sleeping with the mouth open to sleeping with the mouth closed lowers Pcrit by approximately 4 cm H_2O.[12] A 10% weight loss can lower Pcrit by 2 to 4 cm H_2O, whereas a 17% weight loss can lower it by 7.5 cm H_2O. In combination, mouth taping and minimal weight loss can lower Pcrit by 6 cm H_2O. Oral appliance therapy can decrease a patient's Pcrit by 2.3 to 4 cm H_2O, upper airway surgery can decrease it by approximately 3.3 cm H_2O, and positional therapy (eg, supine avoidance) can decrease it by 2.2 cm H_2O. In addition, surfactants may decrease Pcrit by 1.75 cm H_2O.[5]

Algorithms have recently been developed that enable flow data from a standard polysomnogram (PSG) to be used to directly quantify Pcrit values without a catheter.[9,13]

Arousal Threshold

During sleep, the respiratory centers in the brain stem track mechanical constraints (eg, low lung volumes, pharyngeal negative pressure, resistance to airflow) and gas exchange abnormalities (eg, oxygen, pH, carbon dioxide changes), which can trigger arousal. To respond to these derangements in mechanics or gas exchange, a specific threshold of increased respiratory effort is associated with the occurrence of an arousal (Figure 3).

The respiratory arousal threshold is defined as the intrathoracic pressure level at which a given individual has an arousal. Some patients have a high arousal threshold (ie, they sleep through major stimuli), and other patients have a low arousal threshold (ie, they wake up easily). The respiratory arousal threshold is the nadir pressure immediately prior to cortical arousal.

Repetitive arousals perpetuate disturbances in the levels of blood gases and cause sleep fragmentation and deprivation. They also promote cyclical breathing and prevent the establishment and maintenance of more stable, deeper stages of sleep. Most importantly, the change from being asleep to being awake increases basal chemoreflex drive and

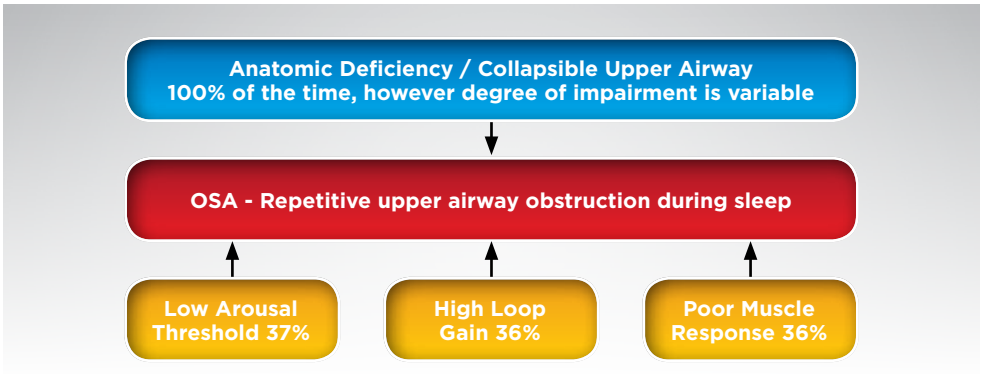

FIG. 1

(1.) Schematic of the four key phenotypes that cause obstructive sleep apnea. All obstructive sleep apnea patients have some degree of impairment in upper airway anatomy (blue box). However, this phenotype varies dramatically between patients. There are also at least three other nonanatomical phenotypes that contribute to OSA pathogenesis, which are collectively present in almost 69% of OSA cases.[10] *Figure 1 provided by Danny Eckert, PhD.*

sensitivity. Arousals from obstructive events can result in a greater degree of hyperventilation that in turn, can lead to hypocapnia and a reduction in ventilatory drive, including the drive to upper airway dilator muscles. In this manner, arousals may perpetuate successive obstructions. The surges of sympathetic neural activity and fragmented sleep associated with arousals can also contribute to cardiovascular disease, metabolic disorders, and neurocognitive deficits.[14] Strategies to reduce the incidence of arousals in these patients may allow for more stable breathing during sleep.

Although most respiratory events are associated with a cortical arousal, and arousals have been considered crucial to reopen the upper airway following a respiratory event in OSA, airway reopening can occur without an arousal as a result of other physiologic functions.

Roughly one-third of OSA patients have a low arousal threshold and may be candidates for targeted therapy.[10] Patients whose OSA is predominantly associated with non-rapid eye movement sleep have greater decreases in ventilation and dynamic changes of $PaCO_2$ during the transition from being awake to this stage of sleep. This finding may be helpful in identifying the clinical subgroup that should undergo treatment to stabilize ventilatory control by raising arousal threshold.[15]

A pharmacologic approach to raising the arousal threshold has been suggested for the low arousal threshold subgroup. Certain medications can be effective in raising the arousal threshold and thus, allowing the accumulation of respiratory stimuli to reach a magnitude sufficient to activate the dilator muscles without triggering arousal.[13] This treatment involves the administration of a non-myorelaxant hypnotic, such as eszopiclone (eg, Lunesta), which can increase the respiratory arousal threshold by 4 to 5 cm H_2O.[16] Although studies have found that raising arousal threshold improves AHI scores in some patients, raising the arousal threshold in patients with unresponsive upper airway dilators may be deleterious because hypoxemia could occur prior to arousal from sleep.

With new algorithms, flow data obtained from a standard PSG can be used to directly quantify arousal threshold without a catheter.[13,17,18] Alternatively, short respiratory event duration is an indicator of low arousal threshold.

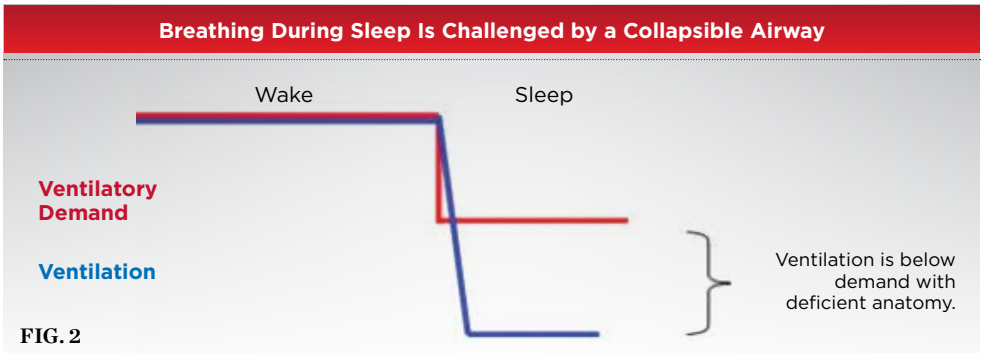

FIG. 2

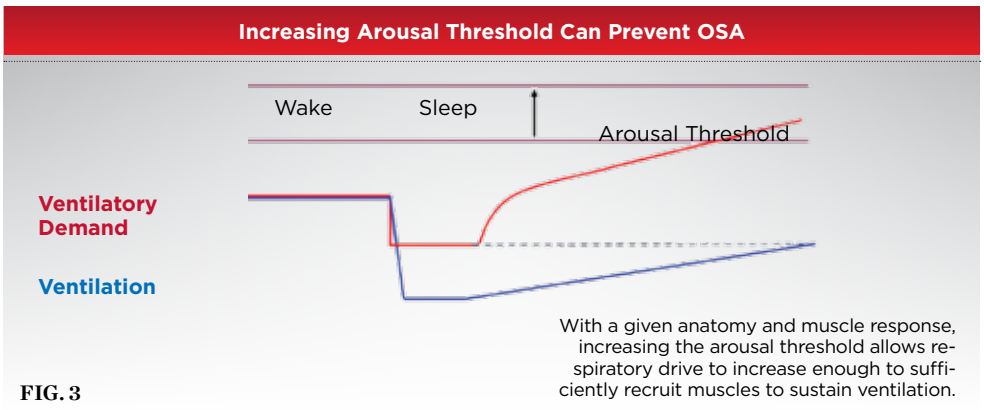

FIG. 3

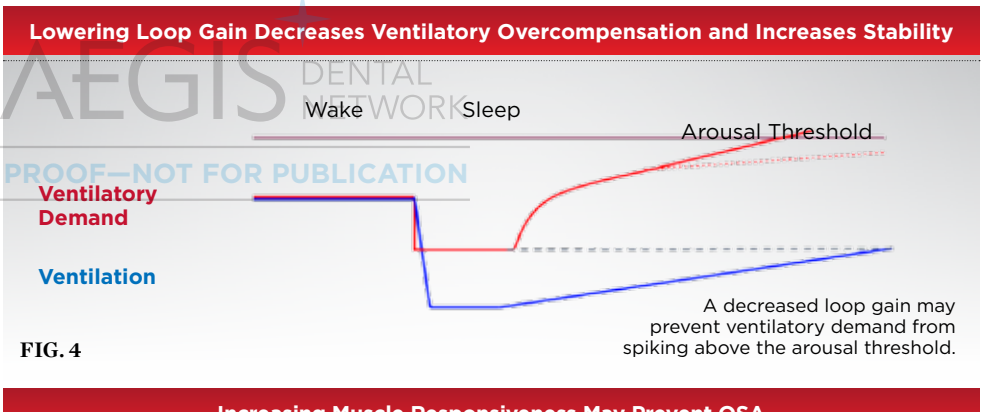

FIG. 4

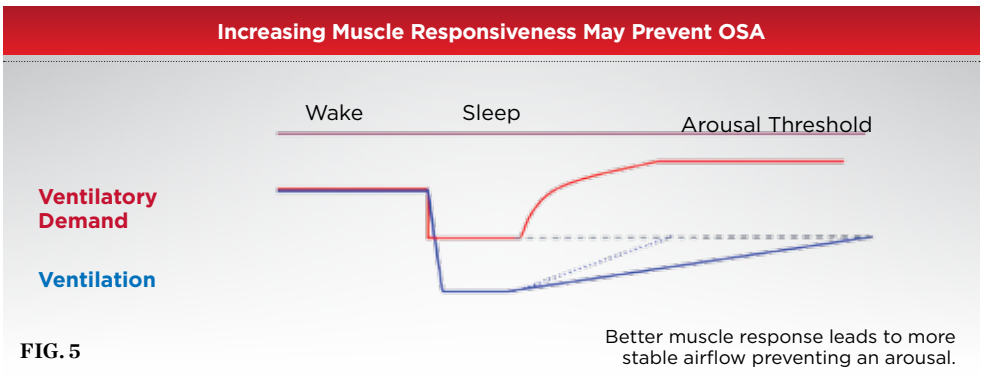

FIG. 5

(2.) There is a decrease in ventilation when patients transition from being awake to asleep, and increased collapsibility due to deficient anatomy can keep the ventilation below the demand. Lowering Pcrit increases ventilation to keep pace with demand. **(3.)** A low arousal threshold is undesirable because the premature arousals prevent the body from building up a healthy respiratory drive. Elevating the arousal threshold prevents early activation of the sympathetic nervous system and sleep fragmentation. **(4.)** Lower loop gain is desirable because it keeps the ventilatory demand in a narrower, more stable range. **(5.)** Increasing the muscle responsiveness has a stabilizing effect on the airway by preventing arousals and shortening the duration of obstructive events. *Figure 2 through Figure 5 provided by Robert Owens MD, University of California, San Diego.*

Loop Gain

Loop gain, which is an engineering term, is a value describing the propensity of a system governed by feedback loops to develop unstable behavior. Ventilation is such a system. Loop gain in a ventilation system measures the stability of the negative feedback chemoreflex control system, calculated as the ratio of the ventilatory response to the disturbance that elicited the response (Figure 4).

This tightly controlled, rapidly responsive negative feedback system between the brain and the lungs allows for stable ventilation with relatively small changes in CO_2 levels. The oscillating $PaCO_2$ levels in the system stay comfortably within a CO_2 reserve of approximately 5 mm Hg.[19]

During sleep, the levels of CO_2 and O_2 in the blood dominate ventilatory control. Arterial CO_2 has the greater influence, and an increase in CO_2 stimulates an increase in ventilatory drive. Ventilatory drive determines not only the level of activity of the thoracic pump muscles but also the upper airway dilator muscles.[14] When the CO_2 level is low as a consequence of hyperventilation, the neural drive to the upper airway muscles is reduced and the upper airway becomes susceptible to collapse.

A low loop gain (ie, < 1) is consistent with stable breathing. The initial ventilatory response may partially correct the changes in blood gas levels, with any residual changes being gradually corrected later. This is a stable response that is considered to have low loop gain.

High loop gain is a consequence of hypersensitive ventilatory control. This occurs when the initial ventilatory response results in an "overcorrection" or "overcompensation" of the changes in gas levels such that they are better than they were before the perturbation. High loop gain is an indicator of less stable control because a disproportionately large ventilatory response will result in a greater degree of hypocapnia and a subsequent reduction in ventilatory drive. In this manner, a high loop gain (ie, > 1) contributes to the perpetuation of apneas.[14]

Predictors of OSA resolution with oral appliance therapy are now available because recent studies have revealed that those who responded well had airways that were less likely to collapse (ie, a more negative Pcrit) and lower baseline loop gain when compared with those who responded poorly. Oral appliance therapy improves upper airway collapsibility by addressing anatomical traits; it does not affect muscle dilator effectiveness, loop gain, or arousal thresholds. Those who responded poorly to oral appliance therapy experienced improvement in their upper airway anatomy and collapsibility, but these patients still had residual OSA due to nonanatomic contributions (ie, high loop gain).

In fact, anatomical treatments for sleep apnea may be ineffective in those with excessively high loop gain. Fortunately, measurement of the underlying loop gain can enable clinicians to provide appropriate alternative therapies to these patients because high loop gain is a modifiable factor in one-third of patients with OSA. In addition, loop gain can be used to predict the effectiveness of surgical procedures.[20] Supplemental O_2 can lower loop gain by 50%, and acetazolamide can lower loop gain by 40% to 50%. The effectiveness of CO_2 stabilization will depend on the baseline value. Algorithms can be used to collect loop gain data from the results of a standard PSG.[13,21]

Muscle Recruitment

The magnitude of the stimuli (ie, from both negative pressure and chemostimulation) required to recruit upper airway dilator muscles adequately to overcome negative intrapharyngeal closing pressures is called the upper airway recruitment threshold (Figure 5). Poor upper airway muscle responsiveness increases the duration of obstructive events because greater stimuli are required to activate the muscles to terminate the obstruction. If the upper airway muscle responsiveness is sufficiently poor, then arousal is necessary to initiate airway opening. The increased chemoreflex drive resulting from both the prolonged obstruction and the accompanying

TABLE 1

Targeted Non-CPAP Interventions for Each of the Phenotypic Traits of OSA[a,b]

Impaired Anatomy (High Pcrit)	Impaired Dilator Muscle Function When Asleep	Respiratory Control Instability (High Loop Gain)	Low Respiratory Arousal Threshold
Mandibular advancement (2.3 cm H_2O ↓ in Pcrit)	Upper airway muscle training (muscle effects unknown, ~50% ↓ in AHI)	Supplemental O_2 (~50% ↓ in loop gain)	Non-myorelaxant hypnotics (4 to 5 cm H_2O ↑ in arousal threshold)
Upper airway surgery (3.3 cm H_2O ↓ in Pcrit)	Hypoglossal nerve stimulation (supra-physiologic stimuli, ~50% to 70% ↓ in AHI)	CO_2 stabilization (variable AHI changes according to baseline respiratory control characteristics)	
Supine avoidance (2.2 cm H_2O ↓ in Pcrit)	Desipramine (prevents the typical ~25% sleep-related reduction in tonic genioglossus activity and ↓ Pcrit by ~2 to 3 cm H_2O)	Acetazolamide (~40% ↓ in loop gain)	
Head extension (13.1 cm H_2O ↓ in Pcrit from flexion to extension)			
Weight loss (7.5 cm H_2O ↓ in Pcrit with a 17% reduction in body mass index)			
Surfactant (1.75 cm H_2O ↓ in Pcrit)			

[a]The size of the change that accompanies each intervention is provided in parentheses. [b]Reprinted from *Sleep Medicine Reviews,* 37, Eckert DJ, Phenotypic approaches to obstructive sleep apnoea – New pathways for targeted therapy, 45-59, Copyright 2018, with permission from Elsevier.

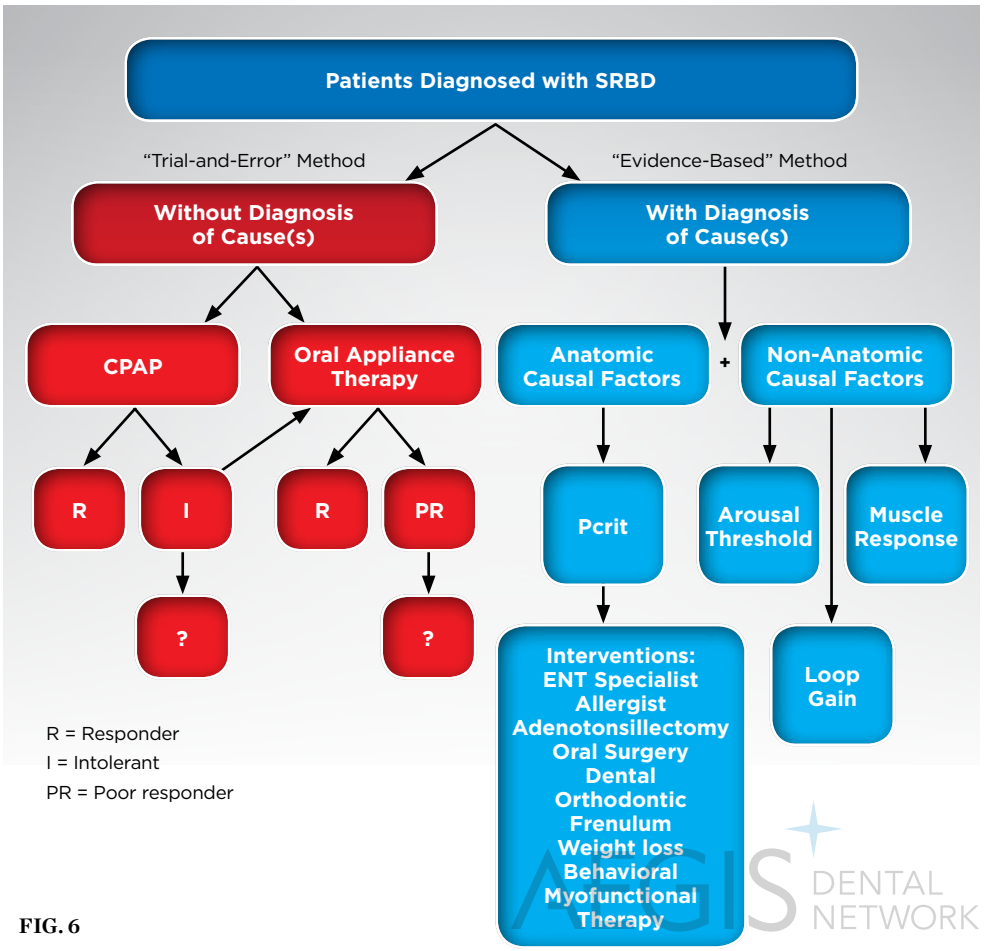

FIG. 6

(6.) An evidence-based approach is the basis of precision medicine. A trial-and-error approach is both time-consuming and much more expensive.

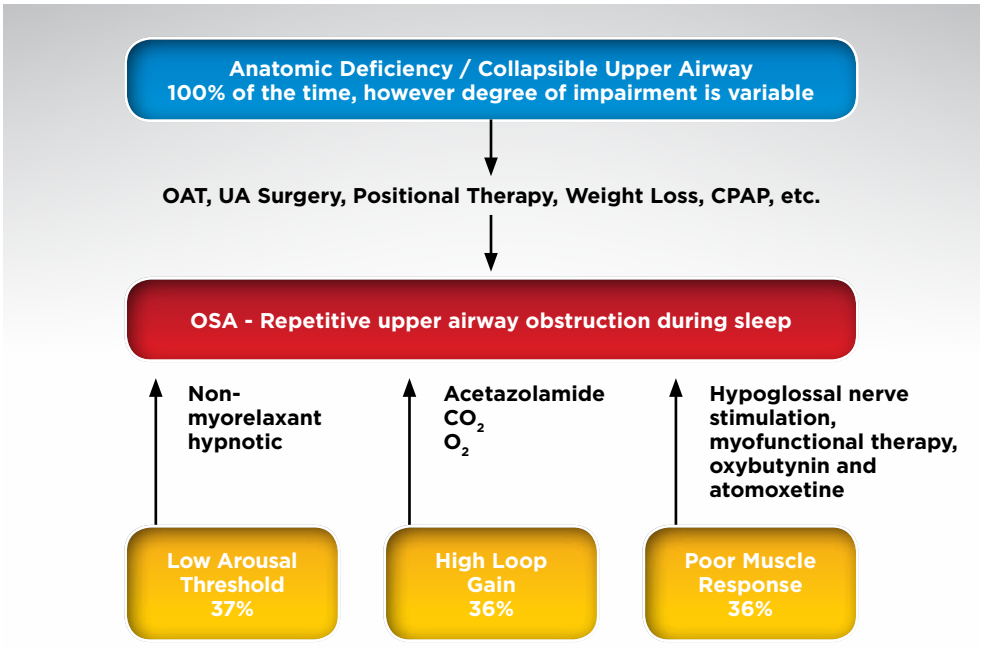

FIG. 7

(7.) Trait-targeted therapy is an important component of precision medicine that is derived from evidence-based diagnosis.

arousal serves to increase the ventilatory response after airway opening. Thus, poor upper airway muscle recruitment interacts with the arousal threshold and loop gain to contribute to repetitive apnea.[14] Interestingly, enhanced upper airway muscle responsiveness is a distinct feature among overweight or obese individuals without OSA.[22]

Improved muscle compensation is associated with a reduction in AHI score. Muscle training can decrease an AHI score by 50%, and hypoglossal nerve stimulation can decrease it by 50% to 70%. Pharmacologic treatments, such as the administration of desipramine, can decrease Pcrit by 2 to 3 cm H_2O, significantly improving genioglossus muscle responsiveness and, consequently, upper airway collapsibility in patients with OSA.[23]

Combining medications such as oxybutynin and atomoxetine boosts responsiveness during non-rapid eye movement sleep. Oxybutynin blocks receptors for acetylcholine on hypoglossal motor neurons, making the genioglossus muscle more responsive during rapid eye movement sleep, and atomoxetine prevents norepinephrine from being resorbed by the neurons that release it, increasing its signal.[24]

Upper airway muscle responsiveness can be evaluated by using algorithms on data collected from a standard PSG.[13,25]

Discussion

The causes of SRBDs are multifactorial, not just anatomically driven; thus, assessments of anatomic and nonanatomic contributions should be used to direct trait-targeted therapies. Trait targets include high Pcrit, low arousal threshold, high loop gain, and poor muscle responsiveness. Because each trait-targeted therapy provides a limited benefit, for cases involving more than one trait, combination therapy may be required to achieve a stable airway (Table 1).[5]

Given the heterogeneity of the causes of SRBDs, it is no wonder that many clinicians have gone down the unscientific path of "trial and error" treatments[26] (Figure 6). New diagnostic methods to measure a patient's underlying physiologic traits using routine clinical sleep study data have removed some of the uncertainty and empowered clinicians to deliver individualized therapy for SRBD treatment (Figure 7).[14,27,28,29] Maintaining a collaborative mindset among dental, medical, and allied health professionals will lead to evidence-based treatment decisions and optimize patient airway and sleep outcomes.

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Evidence-Based Treatment for Sleep-Related Breathing Disorders

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1 **Approximately what percentage of affected patients have at least one nonanatomic trait that contributes a variable influence to their airway function?**

A. 20%
B. 46%
C. 69%
D. 83%

2 **What is an objective measurement of upper airway collapsibility?**

A. Pcrit
B. Arousal threshold
C. Loop gain
D. Muscle recruitment

3 **A Pcrit above what value reflects anatomic compromise?**

A. -8 cm H_2O
B. -7 cm H_2O
C. -6 cm H_2O
D. -5 cm H_2O

4 **A 10% weight loss can lower Pcrit by:**

A. 2 to 4 cm H_2O.
B. 3 to 5 cm H_2O.
C. 1 to 2 cm H_2O.
D. 2 to 3 cm H_2O.

5 **What is defined as the intrathoracic pressure level at which a given individual has an arousal?**

A. Pcrit
B. Respiratory arousal threshold
C. Airway recruitment threshold
D. Loop gain

6 **The surges of sympathetic neural activity and fragmented sleep associated with arousals can also contribute to:**

A. cardiovascular disease.
B. metabolic disorders.
C. neurocognitive deficits.
D. all of the above.

7 **Administration of a non-myorelaxant hypnotic, such as eszopiclone (eg, Lunesta) can increase the respiratory arousal threshold by:**

A. 1 to 2 cm H_2O.
B. 2 to 3 cm H_2O.
C. 3 to 4 cm H_2O.
D. 4 to 5 cm H_2O.

8 **What is a consequence of hypersensitive ventilatory control?**

A. Anatomic impairment
B. Lower Pcrit
C. High loop gain
D. Enhanced muscle responsiveness

9 **High loop gain is a modifiable factor in what proportion of patients with OSA?**

A. One-half
B. One-third
C. One-quarter
D. One-fifth

10 **Muscle training can decrease an AHI score by what percentage?**

A. 10%
B. 30%
C. 50%
D. 70%

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To use our mail-in option, please completely fill out the Answer Form and mail it along with your payment of $32 to the address provided below. **NOTE: THIS FORM MUST BE COMPLETELY FILLED OUT AND INCLUDE YOUR NAME AND PAYMENT INFORMATION IN ORDER TO BE PROCESSED AND CREDIT AWARDED.** Your test will be graded and your certificate will be sent to you in the mail; please allow approximately 2 to 3 weeks for processing. Course valid from 3/1/19 to 3/31/22.

Inside Dentistry®

March 2019

Evidence-Based Treatment for Sleep-Related Breathing Disorders

1	A	B	C	D	6	A	B	C	D
2	A	B	C	D	7	A	B	C	D
3	A	B	C	D	8	A	B	C	D
4	A	B	C	D	9	A	B	C	D
5	A	B	C	D	10	A	B	C	D

☐ **CHECK** (payable to AEGIS Communications)

CREDIT CARD Please complete information and sign below:

Card Number ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Expiration Date: Month/Year ☐☐/☐☐☐☐

CVV Code: ☐☐☐

☐ **VISA** ☐ **Mastercard**

Total amount _____ ($32 per test)

SIGNATURE _____ **DATE** _____

LAST 4 DIGITS OF SSN ☐☐☐☐

ADA Number ☐☐☐☐☐☐☐☐☐☐

AGD Number ☐☐☐☐☐☐☐☐

The Month and Day (not year) **of Birth. Example, February 23 is 02/23** **Month/Date of Birth** _____

NAME _____

ADDRESS _____

CITY _____ E-MAIL ADDRESS _____

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Please mail completed forms with your payment to:
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SCORING SERVICES: By Mail | Fax: 1-215-504-1502 | Phone-in: 877-423-4471 (9 am - 5 pm ET, Monday - Friday)
Customer Service Questions? Please Call 877-423-4471

PROGRAM EVALUATION

Please circle your level of agreement with the following statements.
(4 = Strongly Agree; 0 = Strongly Disagree)

1. Clarity of objectives	4	3	2	1	0
2. Usefulness of the content	4	3	2	1	0
3. Benefit to your clinical practice	4	3	2	1	0
4. Usefulness of the references	4	3	2	1	0
5. Quality of the written presentation	4	3	2	1	0
6. Quality of the illustrations	4	3	2	1	0
7. Clarity of review questions	4	3	2	1	0
8. Relevance of review questions	4	3	2	1	0

9. Did this lesson achieve its educational objectives? Yes No

10. Did this article present new information? Yes No

11. How much time did it take you to complete this lesson? _____ min