Treatment of Obstructive Sleep Apnea

Prospects for Personalized Combined Modality Therapy

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Abstract

Obstructive sleep apnea (OSA) is a common sleep disorder with serious associated morbidities. Although several treatment options are currently available, variable efficacy and adherence result in many patients either not being treated or receiving inadequate treatment long term. Personalized treatment based on relevant patient characteristics may improve adherence to treatment and long-term clinical outcomes. Four key traits of upper airway anatomy and neuromuscular control interact to varying degrees within individuals to cause OSA. These are: (*1*) the pharyngeal critical closing pressure, (*2*) the stability of ventilator chemoreflex feedback control (loop gain), (*3*) the negative intraesophageal pressure that triggers arousal (arousal threshold), and (*4*) the level of stimulus required to activated upper airway dilator muscles (upper airway recruitment threshold). Simplified diagnostic methods are being developed to assess these pathophysiological traits, potentially allowing prediction of which treatment would best suit each patient. In contrast to current practice of using various treatment modes alone, model predictions and pilot clinical trials show improved outcomes by combining several treatments targeted to each patient's pathophysiology profile. These developments could theoretically improve efficacy and adherence to treatment and in turn reduce the social and economic health burden of OSA and the associated life-threatening morbidities. This article reviews OSA pathophysiology and identifies currently available and investigational treatments that may be combined in the future to optimize therapy based on individual profiles of key patient pathophysiological traits.

Keywords: treatment; therapy; continuous positive airway pressure; sleep; sleep apnea

(Received in original form August 18, 2015; accepted in final form November 16, 2015)

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Ann Am Thorac Soc Vol 13, No 1, pp 101–108, Jan 2016

DOI: 10.1513/AnnalsATS.201508-537FR
Internet address: www.atsjournals.org

Obstructive sleep apnea (OSA) is a common sleep disorder increasing in prevalence in the United States and other middle- and high-income countries primarily due to the epidemic of obesity, a major risk factor (1). OSA contributes to the development of serious comorbidities such as diabetes (2), cardiovascular disease (3), stroke (4), and neurocognitive deficits (5). Adequate treatment can improve physiological and metabolic consequences of OSA and possibly increase survival (6–8). Several treatment options are currently available; however, discomfort, stigma, invasiveness, poor efficacy, and high cost result in reluctance to seek treatment and poor long-term adherence to treatment (9).

One factor important for treatment is that OSA is due to the interaction of several key traits of upper airway anatomy and neuromuscular control that contribute to varying degrees within individuals (10), yet each form of treatment currently available primarily targets one trait. Additionally, each patient's specific pathology is not assessed during diagnosis. Thus, choice of treatment is essentially an educated guess, often developed on a trial-and-error basis starting with the gold-standard treatment and trialing others as needed. Positive first experiences with treatment predict increased long-term adherence (9, 11). Therefore, the ability to diagnose a patient's individual pathophysiology and predict which treatments would provide the best outcomes could greatly increase efficacy and long-term adherence.

New diagnostic methods capable of quantifying each trait have been developed, which are technically feasible to implement in routine clinical sleep studies (10, 12). In addition, model estimates and clinical trials show that combination therapy in patients selected by their specific pathology may markedly improve treatment efficacy, potentially resolving OSA in patient populations exhibiting residual OSA with

one treatment alone (12–16). These developments may transform how OSA is treated in the future and have far-reaching implications for reducing the social and economic health burden of OSA and associated life-threatening morbidities. This article reviews OSA pathophysiology, problems with currently available treatment options, and new diagnostic methods that may be used in future to individualize combination therapy.

OSA Pathophysiology

Anatomy

Reductions in pharyngeal lumen size increase collapsibility (measured as the air pressure at which the passive airway collapses [17]). Abnormalities in craniofacial structure can cause OSA even in young, healthy-weight people (18). However, obesity is the biggest contributory factor in the development of OSA in most patients, with the prevalence of OSA increasing from 70 to 95% with increasing body mass index from 40 to 60 kg/m^2 (19).

Fat deposition both around the pharynx and within upper airway dilator muscles such as the genioglossus decreases airway lumen size and causes detrimental changes to upper airway muscle function (20, 21). Abdominal obesity compresses the abdomen and thoracic cavities, reducing lung volume and possibly causing rostral shifting of the diaphragm, which reduces tracheal tension and thus impairs pharyngeal mechanics (22). Therefore, fat deposition around the pharynx and torso both increase airway collapsibility (23). However, the air pressure at which the passive airway collapses accounts for only a small percentage of apnea–hypopnea index (AHI) variability (17). Importantly, interactions of upper airway anatomy with aspects of neuromuscular control predict the severity of OSA (24, 25). Nonanatomical traits contribute to the pathogenesis of OSA in many patients (24), as will be discussed (Table 1).

Loop Gain

During sleep, ventilatory control is dominated by the level of CO_2 and O_2 in the blood. Arterial CO_2 has the greater influence, with increasing CO_2 stimulating 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. Consequently, the upper airway is susceptible to collapse when CO_2, and therefore neural drive to the upper airway muscles, is low (26).

Loop gain is an engineering method used to measure the stability of the negative feedback chemoreflex control system, calculated as the ratio of the ventilatory response to the disturbance that elicited the response (Table 1). Higher loop gain defines less-stable control, as a disproportionately large ventilatory response will result in a greater degree of hypocapnia and subsequent reduction in ventilatory drive. Thus, high loop gain contributes to perpetuating apneas (27).

Supporting this concept is evidence that patients with OSA have higher loop gain than patients without OSA and that loop gain predicts AHI (28, 29). Independent of factors known to alter chemoreflex control, such as weight, patients with OSA exhibit abnormalities in chemoreflex control that increase loop gain (25, 30, 31). These abnormalities normalize with continuous positive airway pressure (CPAP) treatment (31–33), indicating they are induced by OSA itself. Obesity-dependent reductions in lung volume may also alter ventilatory control (28, 34, 35).

Arousal Threshold

Increasing negative intraesophageal pressure during airway obstruction triggers arousal, and the change from sleep to wake increases basal chemoreflex drive and sensitivity (36–38). Consequently, obstructive events terminated by arousal result in a greater degree of hyperventilation and consequent hypocapnia and reduction in ventilatory drive, including drive to upper airway muscles (39). Thus, arousals may perpetuate successive obstructions.

A high arousal threshold (aroused by more negative pressures) appears to develop in many patients with OSA as an adaptive mechanism (40), as a greater magnitude of both negative pressure stimuli and chemostimulation can accumulate to recruit upper airway dilator muscles to terminate the event before arousal. Arousals also result in surges in sympathetic neural activity and fragmented sleep, contributing to cardiovascular disease, metabolic disorder, and neurocognitive deficits (41–43). Therefore, a low arousal threshold may contribute to obstructive events and to OSA-associated morbidities (Table 1).

Upper Airway Recruitment Threshold

The magnitude of stimuli (both negative pressure stimuli and chemostimulation) required to recruit upper airway dilator

Table 1. Four physiological traits causing obstructive sleep apnea that may be targeted with future personalized treatment modalities

Trait	Description	Treatments
Pcrit	Pharyngeal critical closing pressure	Positive airway pressure surgery, mandibular advancement splint, positional therapy weight loss
Loop gain	Stability of ventilatory chemoreflex feedback control	O_2 and CO_2 supplementation, pharmacological agents to reduce plant gain (acetazolamide) and/or controller gain (antioxidants)
Arousal threshold	Negative intraesophageal pressure that triggers arousal	Sedatives
Upper airway recruitment threshold	Level of stimuli required to activate upper airway dilator muscles	Hypoglossal nerve stimulation, chemical upper airway muscle stimulation

Definition of abbreviation: Pcrit = air pressure at which the passive airway collapses.

muscles adequately to overcome negative intrapharyngeal closing pressures is called the upper airway recruitment threshold (25) (Table 1). Poor upper airway muscle responsiveness increases the duration of obstructive events, as 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 (25). Increased chemoreflex drive due to both prolonged obstruction and arousal increases the ventilatory response after airway opening (25, 39, 44). Thus, poor upper airway recruitment interacts with arousal threshold and loop gain to contribute to repetitive apnea.

Treatment Options

Targeting Anatomy

CPAP. The first-line, gold-standard treatment for OSA is CPAP treatment, which supplies air flow through a mask to splint the airway open. CPAP is the only common treatment that, if tolerated, can effectively eliminate apneas in all patients and has been shown to improve metabolic and cardiovascular consequences of OSA and possibly to increase survival (6, 8, 45, 46).

However, many patients are unable to tolerate CPAP long term (9). Patients commonly complain of inability to breathe out as the constant positive pressure causes discomfort during passive exhalation. CPAP (without adequate humidification) also dehydrates the mucous membranes, resulting in common complaints of dry mouth and nose and blocked sinuses (47). Most devices are now able to warm and humidify the inflowing air, but humidification causes sweating within the mask. This situation could create a breeding ground for bacterial and fungal infections, theoretically increasing the risk of sinus and respiratory infections in CPAP users (47, 48). Ill-fitting masks tend to leak, resulting in inadequate pressure to maintain airway patency, eye irritation, and disruption to sleep (49, 50). In addition, wearing a mask to sleep is not exactly considered attractive, and particularly young single patients may avoid diagnosis and treatment for fear of potential negative social impact of CPAP use (51) (Table 2).

Upper airway surgery. Several surgical procedures exist to enlarge the diameter of the upper airway. Different procedures target different structures and levels of the airway. These procedures include nasal surgery to reduce resistance, tonsillectomy, radiofrequency ablation of the tongue base or palate, surgical advancement of the mandible, or more extensive surgeries to change the structure and dimensions of the upper airway (52).

Surgical treatment is invasive, and efficacy cannot be reliably predicted with imaging or preoperative screening. In some cases, OSA is actually worsened after surgery, which, unlike other treatment methods, is nonreversible (52) (Table 2). However, surgery has the advantage of removing the issue of adherence to treatment (which frequently complicates CPAP therapy); thus, a subset of patients have excellent outcomes with upper airway surgery.

Mandibular advancement splints. Several types of oral appliances that advance the mandible are available for the treatment of both OSA and snoring. These devices increase the dimensions of the pharyngeal cross-sectional area and reduce airway collapsibility (53, 54). Mandibular advancement splints (MAS) have appeal to many patients due to ease of use and being less invasive than both CPAP and surgery. Therefore, long-term compliance is quite high, ranging from 50 to 100% (55). However, approximately 40% of patients using MAS still exhibit clinically elevated AHIs (55) (Table 2). Tooth and jaw pain, dry mouth, and hypersalivation are common complaints, although high observed compliance implies that MAS are well tolerated (56, 57). Long-term use can also cause subtle dental and facial structural changes, which appear to worsen progressively over time (57–59).

Positional therapy. Approximately half of patients exhibit an AHI that is at least twice as high in the supine position than in other positions, called supine-dependent OSA (60). Supine position increases airway collapsibility due to changes in pharyngeal dimension and abdominal compression (22, 61). Techniques to discourage supine sleep have therefore been tested, with somewhat variable results. Lateral sleep usually does not eliminate OSA, and patients habituate and eventually sleep supine with positional therapy (62, 63) (Table 2). Although longitudinal data are limited, studies show adherence is poor due to discomfort, frequent awakenings, and lack of perceived effectiveness (60, 64).

Weight loss. Obesity is one of the key risk factors for the development of OSA, and sufficient weight loss can eliminate OSA entirely (65). Surgical, dietary, and exercise interventions have all shown significant

Table 2. Limitations of currently available single mode therapies

Treatment	Limitations
Positive airway pressure	Discomfort Dry mouth and nose, congested sinuses Air leaks causing irritation and disrupted sleep Negative social impact
Surgery	Invasive Inability to predict outcome Irreversible Expensive Can worsen OSA
Mandibular advancement splints	Reduces but rarely resolves AHI Tooth and jaw pain Hypersalivation Dental and facial deformation with long term use
Positional therapy	Reduces but rarely resolves AHI Discomfort Lack of perceived effectiveness
Weight loss	Lack of effective weight loss strategies Lack of longitudinal data
Hypoglossal nerve stimulation	Invasive Expensive and limited life span Post-surgery mean AHI often remains clinically elevated

Definition of abbreviations: AHI = apnea–hypopnea index; OSA = obstructive sleep apnea.

Table 3. Investigational new therapies

Treatment	Potential Application
O_2	Blunts carotid chemosensitivity and reduces loop gain
CO_2	Selective application during hyperventilation can prevent hypocapnia and ventilatory depression
Acetazolamide	Reduces plant gain by preventing excretion of CO_2
Antioxidants	Can reduce AHI, arousals, and systemic oxidative stress
Sedatives	Nonmyorelaxant sedatives such as eszopiclone and trazadone increase arousal threshold, thereby reducing AHI
Topical upper airway stimulants	Experimental agents may increase reactivity of upper airway dilator muscles to excitatory stimuli and decrease upper airway recruitment threshold
Combination therapy	Diagnosis of which traits patients exhibit deficits in may allow the combination of therapies (existing and currently experimental) targeting those traits to provide a more effective treatment tailored to the individual patient's pathology

Definition of abbreviation: AHI = apnea–hypopnea index.

reductions in AHI. However, longitudinal data are lacking, and therefore whether weight loss is maintained and its effects on OSA are uncertain (1, 66) (Table 2). OSA is now considered another aspect of metabolic disorder, the coexistence of both conditions being called "syndrome Z" (67). Further research into metabolic disorder and effective weight loss strategies is required to treat and to prevent OSA.

Targeting Loop Gain

O_2 and CO_2. As hyperoxia blunts carotid body basal activity and responsiveness to hypercapnia, supplemental oxygen has been shown to decrease AHI by approximately 50% via a reduction in loop gain in patients with OSA with high loop gain. This effect on AHI is not simply a function of elevating oxygen tensions but is related to oxygen's effect on stabilizing control of breathing. However, supplemental oxygen has no significant effect on AHI in patients with OSA with low loop gain (68). Similarly, supplementing CO_2 only during the hyperventilation phase reduces AHI via stabilizing ventilatory chemoreflex control. This was only found effective in patients with abnormalities in chemoreflex control that increase loop gain (31, 69, 70) (Table 3).

Pharmacological agents. Acetazolamide is a carbonic anhydrase inhibitor shown to reduce AHI by approximately 50% via a reduction in loop gain (71, 72). This effect was seen in all patients, regardless of high or low loop gain. Acetazolamide seems to reduce loop gain by reducing plant gain (reducing the effectiveness of the lungs to alter blood gases) (72). Clinical trials will be required to determine whether acetazolamide improves important hard outcomes in select patients with OSA.

Antioxidants. The abnormalities in chemoreflex control exhibited in patients with OSA are also reduced with 1 to 5 months of CPAP treatment (31–33). These abnormalities are likely induced by repeated exposure to intermittent hypoxia via neuroplasticity (induced change to neural function) of chemoreceptors and ventilatory motor neurons (73). Intermittent hypoxia-induced ventilatory neuroplasticity is dependent on the formation of reactive oxygen species and antioxidant treatment before intermittent hypoxia blocks the development of ventilatory neuroplasticity (74, 75). Therefore, antioxidant treatment in patients with OSA may also be used as a treatment to reduce loop gain and AHI.

In support of this concept, two studies have shown that antioxidant treatment without CPAP reduces OSA severity (76, 77). Although reductions in AHI in both studies may not be considered clinically relevant, both studies also showed significant reductions in arousals and oxidative stress (76, 77). Many of the life-threatening morbidities associated with OSA are due to frequent arousals, which fragment and restrict sleep, and increased exposure to intermittent hypoxia-causing systemic oxidative stress (42, 78). Therefore, the number of apneic episodes may not be so relevant if arousals and oxidative stress plus associated consequences are alleviated.

Targeting Arousal Threshold

Sedatives. As arousal stimulates hyperventilation, pharmacological treatments to increase the threshold of stimuli required to elicit arousal have also been investigated in OSA therapy. Pharmacological agents such as eszopiclone, trazodone, and donepezil have been found efficacious in reducing AHI in patients with OSA (79–81).

Eszopiclone and trazodone were both found to reduce AHI via increasing the arousal threshold and reducing time spent in N1 sleep (light sleep) (81, 82) (Table 3). Whether donepezil reduces AHI by increasing the arousal threshold is not certain and is currently under investigation. Sedative treatment in OSA is limited to patients with adequate upper airway recruitment thresholds exhibiting mild oxygen desaturations, because suppressing arousals may be theoretically deleterious if prolonged apneas result.

Targeting Upper Airway Recruitment Threshold

Hypoglossal nerve stimulation. The hypoglossal nerve innervates the genioglossus and other upper airway dilator muscles and therefore plays a critical role in modulating upper airway muscle activity and airway patency. Several implantable devices that activate upper airway dilator muscles to prevent obstruction have been developed. A recent metaanalysis found no significant differences in outcomes between devices, with significant reductions in AHI of 50% at 12 months' follow up (83). However, mean AHI remained elevated at greater than 15 events/h (83) (Table 2). An additional limitation to this technology is that devices can cost $30,000, with need for replacement batteries and a short life span of approximately 5 to 15 years (84).

Chemical upper airway stimuli. Mild hypercapnia reduces AHI by increasing ventilatory drive and activating upper airway dilator muscles (70) (Table 3). This is a simple, noninvasive treatment that could be delivered via nasal cannula in the home

Table 4. Summary of key points

Currently there is no method to predict which treatments will have the best outcomes in individual patients.
Methods have been developed to quantify deficits of specific traits contributing to OSA in the individual.
Model estimates predict combination therapy targeted to a patient's specific pathology may successfully treat 50–80% of patients without CPAP.
These methods are theoretically possible to implement in routine clinical care.
Clinical trials are required to validate the efficacy and feasibility of implementing these methods in clinical practice.

Definition of abbreviations: CPAP = continuous positive airway pressure; OSA = obstructive sleep apnea.

setting. CO_2 can induce insomnia and catecholamine release, and long-term exposure may induce other deleterious metabolic consequences; thus, its clinical use is limited (85).

A topical potassium channel blocker (AVEO118) has been tested in an anesthetized pig model of OSA, which reduced the recruitment threshold of the genioglossus (activated at more positive pressures) and inhibited upper airway collapse in a dose-dependent response (86). If proven effective in humans, this approach would yield a novel, noninvasive mechanism to reduce upper airway recruitment threshold, a trait of OSA that has previously been difficult to target.

Combination Therapy

Evidence of Efficacy

As each treatment option primarily targets only one trait, poor efficacy for single-modality therapy is likely due to the other traits not being modulated (81). Thus, combining therapies to target several individual patient traits could theoretically improve treatment efficacy. In support of this concept are clinical trials showing resolution or marked improvement of AHI with combination therapy in patients selected based on their individual pathophysiology.

In patients exhibiting residual supine-dependent OSA with an MAS, the combination of MAS with supine avoidance therapy significantly reduced AHI compared with either treatment alone (13). From a median baseline AHI of 20.8/h (interquartile range, 15.1–33.6), MAS alone reduced AHI to 11.0/h (6.7–13.8) and supine avoidance therapy to 11.1/h (3.5–17.7). Combined, AHI was reduced to 5.7/h (3.6–7.4) (13).

Oronasal CPAP is less effective than nasal CPAP, believed to be due to posterior mandibular displacement caused by oral breathing. In patients exhibiting obstruction with an oronasal mask at higher pressures than required to resolve OSA with nasal mask, the combination of oronasal mask CPAP with MAS effectively reduced the pressure required to resolve OSA (14).

As nasal obstruction contributes to poor CPAP efficacy and adherence, nasal surgery can improve compliance and may reduce the effective CPAP level required (15). The addition of MAS in patients exhibiting residual AHI after upper airway surgery has also been shown to reduce AHI significantly from 26.0 ± 7.5/h to nearing clinical resolution of 6.0 ± 0.7/h (16). Other factors, such as sleep quality and minimum oxygen desaturation, also significantly improved.

Individualizing Combination Therapy

Evidence for enhanced efficacy with combination therapy has led to an increase in its implementation in clinical practice. However, currently there are no specific criteria to determine which treatments or combinations of treatments would best suit each patient. Often patients receive a trial of CPAP and, failing that, other treatment options are either trialed alone or added. Presently, selection of treatments is essentially an educated guess, guided by observation and patient tolerance to certain treatments rather than specifically targeting the OSA pathophysiological traits in which individual patients show deficits. Positive first experiences with treatment increase acceptance and long-term adherence to therapy (9, 11). Therefore, ability to predict which treatments and combinations of treatments would provide greatest efficacy for each patient may increase treatment success.

This concept has led to the development of various methods to quantify deficits in each trait contributing to OSA (10). One method uses intermittent CPAP drops conducted during sleep (10). Sleep technologists already capable of titrating patients on CPAP could theoretically conduct these measurements during clinical titrations. Technologically, equipment used in the clinical setting would need to be adapted to allow accurate measurements of ventilatory parameters such as ventilation and mask pressure. Efforts for clinicians to be able to perform these assessments routinely in the clinical setting are underway (12).

A recent study using this method quantified physiological traits in 57 patients, and using data from clinical studies the magnitude by which each trait can be manipulated by currently available treatments was incorporated into a model, allowing prediction of patients who can be successfully treated with either single therapy or combinations of non-CPAP treatments (12). This study predicted that approximately 25% of patients might be successfully treated by manipulating one trait. However, by combining therapies to target two or three traits, the model predicted that approximately 50 to 80% of patients can be successfully treated without CPAP (12) (Table 4).

Experimental studies need to be conducted to validate this treatment approach. However, these model estimates support the concept that treatment efficacy may be vastly improved with already existing treatment options, by first diagnosing which pathophysiological traits the individual patient exhibits and then by combining treatments targeting those specific traits. Although much work is required before these methods can be implemented in clinical practice, these developments are paving the way to reform OSA clinical care, allowing for personalized treatment targeted to the patient's specific pathology.

Conclusions

OSA is now recognized to be due to deficits in several key patient physiological traits, which interact to different degrees in each patient. Although a multitude of treatment options exist, efficacy and long-term adherence to all are suboptimal. This

may be partly due to current treatments primarily targeting only one trait and the inability to predict which treatments would best suit each patient.

Recent developments of simplified techniques to quantify each trait, which could theoretically be implemented in routine diagnostic studies (10), and a model that can predict which patients may be successfully treated with non-CPAP therapies (12) provide the necessary tools to advance how OSA is treated.

Theoretically, these developments could allow providers to identify which treatments and combinations of treatments would benefit each patient, rather than working on a trial-and-error method. Positive experiences with first trial of treatments have been shown to improve long-term adherence to therapy (9, 11). Therefore, implementing this more mechanistic diagnostic and treatment approach into routine clinical practice has the potential to enhance both efficacy and long-term adherence to OSA treatment and significantly reduce the social, economic, and health burden of OSA. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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