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REVIEW ARTICLE

Obstructive Sleep Apnea: New Concepts, Mechanism, and Therapy

[1]Sonam Spalgais, [2]Dipti Gothi

ABSTRACT

Continuous positive airway pressure (CPAP) is the gold standard for the management of obstructive sleep apnea (OSA). However, studies have shown that only around half use the device at the minimum recommended level of ≥4 hours/night. The compliance further drops to 17% after 5 years. Thus, there is need to develop and apply new modalities for the OSA. Also, if the treatment of OSA is directed toward the mechanism, the results are likely to be better. This review is aimed at mechanism-directed treatment for OSA.

Keywords: Mechanism, Newer treatment, Obstructive sleep apnea.

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INTRODUCTION

The mainstay of OSA treatment has been CPAP delivered by an interface to pneumatically splint open the airway to prevent collapse. Many patients are unable to tolerate and initiate CPAP treatment and of those who do, only half of them use the device at the minimum recommended level (≥4 hours/night);[1] furthermore this drops to 17% after 5 years of treatment.[2] However, OSA is increasingly recognized as a heterogeneous disorder with multiple pathophysiological causes. Targeting OSA treatment to individual pathologies could broaden treatment options for the patient and improve patient acceptance, outcomes, and help move toward a future of a personalized medicine approach to treatment.[3] The mechanisms are classified as anatomical mechanism, neuromuscular mechanisms, lung volume, ventilator control stability, low arousal threshold, sleep-related decrease in lung volume, and fluid redistribution as well as upper airway surface tension. Thus, to make treatment more tailor-made and appropriate for a particular patient, new treatment based on pathogenesis and phenotypes have emerged. In this review, we discuss various personalized treatment strategies for OSA as per various pathophysiology and phenotypes.

[1]Assistant Professor, [2]Professor

[1]Vallabhbhai Patel Chest Institute, New Delhi, India

[2]Department of Pulmonary Medicine, Employees' State Insurance Post Graduate Institute of Medical Sciences & Research, New Delhi, India

Corresponding Author: Dipti Gothi, Professor, Department of Pulmonary Medicine, Employees' State Insurance Post Graduate Institute of Medical Sciences & Research, New Delhi India, e-mail: diptigothi@gmail.com

Mechanisms

Anatomical Mechanism

The OSA patients tend to have smaller pharyngeal airways, with a narrower cross-sectional area of the airway lumen, which is more collapsible.[4,5] This is attributed by the surrounding structure including upper airway soft tissues, regional adipose tissue, and the craniofacial skeleton. The collapsing pressure from surrounding pharyngeal tissues is generated by the interaction of pharyngeal soft tissues and the surrounding craniofacial skeletal.[6] Starling Resistor model explained that excess tissue within the bony enclosure must be present to generate sufficient tissue pressure to collapse the airway lumen. This extraluminal tissue pressure can be achieved by either an excess of soft tissue within a normal bony enclosure or by a normal amount of tissue compressed into a reduced enclosure.[6,7] Another anatomical mechanism in OSA is position dependency. The supine posture of body is associated with more as well as worsening of obstructive respiratory events. The upper airway is more collapsible in the supine than in lateral position and this may relate to effects of body position and gravity on airway geometry, upper airway dilator muscle responsiveness, and lung volume.[3,8,9] The various treatment options for the above mechanism of OSA are mandibular advancement devices (MADs), pillar, weight reduction, upper airway surgeries, and positional therapy.

Neuromuscular Mechanisms

The patency of the upper airway depends on the muscular work coordinated between the pharyngeal dilator muscles and the inspiratory muscles. The most important muscle is the genioglossus.[7,10] The upper airway dilator muscle activity is regulated by chemoreceptors, mechanoreceptors, and baroreceptors that detect the

type of change within the upper airway.[11,12] The genioglossus muscle activation is negatively correlated with upper airway collapsibility and pharyngeal resistance.[13] The OSA patients have increased dilator muscle activity during wakefulness, suggesting that a neuromuscular compensatory mechanism exists to counteract collapsing forces.[14] The increase in dilator muscle activity helps to stabilize the airway during the event of negative intraluminal suction pressure which would otherwise make the airway vulnerable to closure. This negative pressure reflex appears to be stronger in OSA patients in the wakeful state.[15] Therefore, the disturbances in upper airway dilator muscle control are clearly a pathogenic mechanism in OSA patients. The treatment options of OSA with neuromuscular mechanisms are hypoglossal nerve stimulation (HNS), oropharyngeal exercise, and serotonergic/cholinergic drugs.

Role of Lung Volume

The upper airway structure and function are also influenced by lung volume. Lung volume falls with sleep and in recombinant position.[16] The increased lung volume improves upper airway patency, reduces collapsibility, airflow resistance, and increases pharyngeal cross-sectional area.[17-19] Furthermore, increased lung volume in OSA patients reduces therapeutic CPAP pressure requirement.[18] Therefore, reduced lung volumes negatively impact on airway patency and contribute to sleep disordered breathing. The primary effect of lung volume on the upper airway may be through mechanical effects by caudal traction that leads to stiffening of upper airway structures. Tracheal traction via mechanical linkage to mediastinal structures in response to increasing lung volume and intrathoracic pressure improves upper airway patency and resistance.[20,21] This increased lung volume also results in caudal traction on the trachea, which increases the pharyngeal lumen size and decreases pharyngeal extraluminal tissue pressure, which may be mediated through caudal movement of the hyoid bone.[7,22] The obese OSA patients have a greater reduction in end expiratory lung volume and diaphragm activity at sleep. Reduced lung volume secondary to obesity may contribute to increased propensity of upper airway collapse. Nasal expiratory positive airway pressure (nEPAP) and weight reduction are treatment option to treat OSA with etiological mechanism of reduced lung volume.

Ventilatory Control Mechanisms

The neuronal output of respiratory center controls breathing to maintain optimal levels of oxygen and CO_2; however, instability in this control system may lead to periods of cyclic breathing and an obstructed airway.[23] It has been well documented that there is greater instability of the ventilatory control system among the OSA patients.[24,25] The chemoreceptor control system, therefore, plays an important role in determining whether obstructive events are followed by unstable breathing, which further exacerbates the problem.[26] The ventilatory instability has been described in terms of "loop gain" which describes the stability of a negative feedback control system in terms of the ratio of the response to a given disturbance.[27,28] The important components of loop gain in control of breathing are chemoresponsiveness of the system. High loop gain reflects an excessive reaction to a disturbance which ultimately leads to instability and fluctuations of hyper- and hypoventilation,[23] while low loop gain reflects a more controlled response to perturbation and ultimately more stable breathing. The strongest correlation between loop gain and apnea/hypopnea index (AHI) occurs in those with a relatively less collapsible airway.[25] So, the instability of ventilatory control, or high loop gain, is an important pathogenic mechanism in OSA patients. The OSA patients with this mechanism benefit when treated with oxygen therapy and respiratory stimulant like acetazolamide.

Role of Arousal Threshold

The obstructive events are generally terminated by arousal from sleep leading to airway opening. So, arousals have been considered a protective event, which terminates apnea and resumes airflow. However, a respiratory event can be terminated without involving an arousal and other neuromuscular and respiratory compensatory mechanisms can increase dilator muscle activity in response to obstruction and open the airway.[29,30] In some cases, termination of a respiratory event with an arousal can be unfavorable, with airway opening and subsequent decrease in airway resistance, leading to hyperventilation and hypocapnia.[29,31] As a result, it reduces upper airway dilator muscle activation, leading to further airway collapse and CO_2 level may decrease below the apnea threshold.[32,33] An arousal occurs before there is time for physiological signals from CO_2 and negative pressure to accumulate and activate dilator muscles and ongoing ventilatory instability occurs in OSA patients due to low arousal threshold.[26] Few studies have shown that patients of OSA with arousal threshold mechanism may benefit more, when treated with non-benzodiazepine sedatives like eszopiclone and zopiclone.

Role of Surface Tension

The adhesive forces between the mucosal surfaces of the upper airway contribute to collapse and high surface tension, which further opposes reopening of the upper airway following closure.[3] The exogenous surfactant

improves upper airway patency by reducing surface tension and improved closing pressures of almost 2 cm H_2O.[34] It was shown that in OSA patients, the upper airway lining liquid has a higher surface tension.[35] Therefore, surface tension of the upper airway mucosa may facilitate or protect the upper airway from collapsing in individuals.[3,36] So, patients with OSA of this phenotype are better with exogenous surfactant and nasal breathing in combination with other therapies.

Role of Rostral Fluid Shift

The observation of high prevalence of OSA in patients with fluid retaining states, such as heart and renal failure leads to the role of nocturnal rostral fluid shift in the pathogenesis of sleep apnea.[37,38] The concept being that, during the day, when the body is predominantly in upright position causes fluid to pool in lower limbs; however, during night in the supine position, gravity acts to move the accumulated leg fluid rostrally and subsequently increase the neck region fluid volume. It leads to increase in tissue pressure and collapsibility of the pharyngeal airway. It has been observed in studies that application of lower body positive pressure results in an increase in neck circumference and decrease in cross-sectional area of the pharyngeal airway, increases in resistance and overall increase in collapsibility.[39,40] The increase in pharyngeal resistance in response to lower body positive pressure is greater in OSA compared with non-OSA patients.[41] The shifting of overnight fluid from the legs to the neck is strongly correlated with AHI in OSA patients.[42] However, the differences in the effect of fluid shift on OSA and lower body positive pressure on upper airway collapsibility were more in male than in female patients.[43,44] The different pattern of rostral fluid movement between male and female may be one mechanism that explains the gender difference in OSA prevalence. The treatment options for patients with this mechanism of OSA are compression stockings, exercise and diuretics in combination with CPAP and others. The overall various mechanism of OSA with their treatment options is summarized in Table 1.

Newer Treatment Options

Mandibular Advancement Devices

One of the new treatment options for OSA patient is MAD. The MAD is an oral appliance, which holds the jaw in a forward position during sleep. This jaw adjustment causes upper displacement of hyoid bone, lateral displacement of parapharyngeal fat pads, and anterior movement of the muscles of the base of tongue. So, MAD increases the size of the upper airway space, increases neuromuscular activation of upper airway and decreases extraluminal tissue pressure.[45,46] The MAD decreases in AHI and symptoms of sleepiness in OSA. However, MAD is more effective in patients with following characteristics, such as, mild-to-moderate OSA, young age, female gender, small neck size, retrognathic jaw, and low body mass index (BMI).[47-49] The American Academy of Sleep Medicine and American Academy of Dental Sleep Medicine recommended MAD for OSA patients, who are intolerant/noncompliance with CPAP therapy.[50] The MAD is a US Food and Drug Administration (FDA)-approved treatment option for patients OSA with noncompliance/intolerant to CPAP treatment. MAD are less effective for patients with morbid obesity (BMI>40), steep mandibular plane, long neck, poor dentition, and acute temporomandibular joint dysfunction. The adverse effects commonly seen with MAD are temporomandibular syndrome, tooth pain and myofascial pain, excessive salivation, dryness of the mouth, overbite, and reduction of the protrusion.[3,49,51] Overall, MAD is less effective than CPAP therapy to treat OSA patients. However, the efficacy of the MAD may come to similar to CPAP due to its better adherence rate.[7,52-54]

Table 1: Possible various mechanism and their treatment options

Mechanism of OSA	*Possible etiologies*	*Treatment options*
Anatomical	Narrow, small, and collapsible upper airway, obesity, adipose tissue deposition, enlargement of soft tissues, and craniofacial bony abnormalities	Mandibular advancement devices, pillar, weight reduction, upper airway surgeries, positional therapy
Neuromuscular	Decreases in upper airway dilator muscle tone and reflexes, coordination of dilator and inspiratory muscles, and receptor regulatory muscular activity	Hypoglossal nerve stimulation, oropharyngeal exercise, and serotonergic/cholinergic drugs
Lung volume	Mechanical effect of traction, supine position and obesity	Nasal expiratory positive airway pressure and weight reduction
Ventilatory control	Loop gain mechanism: Instability of ventilator control system, receptor regulatory in changes to O_2 and CO_2 concentration	Oxygen therapy and acetazolamide
Low arousal threshold	Awakening in response to obstructive events	Eszopiclone and zopiclone
Rostral fluid shift	Fluid retention state and positional shifting of fluid	Compression stockings, exercise, and diuretics
Surface tension	High surface tension of upper airway liquid lining	Surfactant and nasal breathing

Pillar Procedure

Pillar is an implant used for the treatment mild and moderate OSA. The pillar procedure is a minimally invasive palatal stiffening technique, usually performed under local anesthesia. It consists of three pieces of polyethylene, which are inserted in a parallel fashion in the soft palate. This causes a chronic inflammatory response that creates a fibrous capsule around them to add structural support, harden the soft palate, and leads to reduced airway vibration and collapse.[7,55,56] There is reduction in AHI, the intensity of snoring, and daytime excessive sleepiness with pillar implant treatment. The effectiveness is more in the patients who do significant palatal component to OSA.[57,58] The risk of postoperative complications and other morbidities is low, as it is a minimally invasive procedure. Patients with lower preoperative BMI and AHI have better long-term response rate.[59-61] So, pillar implant is one of good treatment options for patient of OSA who refuse or fail CPAP therapy.

Pharmacotherapy for Weight

Nearly 60 to 70% of OSA patients are overweight, and about 58% of moderate-to-severe OSA cases are attributable to excess weight.[62-64] Weight loss has been shown to reduce severity of OSA, improve oxygen saturation, quality of life, and sleep parameters.[62,65,66] The beneficial effects of weight loss persist over the long term despite weight regain in OSA patients.[67,68] The clinical practice guidelines recommend weight loss for OSA patients with excess weight.[69,70] Liraglutide is a glucagon-like peptide-1 receptor agonist that was initially approved by the FDA management of type 2 diabetes.[62,71] Liraglutide has recently received approval for weight loss agent at the dose of 3.0 mg once daily.[62,72] The mechanism of action of liraglutide is through appetite suppression, delayed gastric emptying with a subsequent decrease in energy intake.[62,72,73] Blackman et al[62] in a study have shown that liraglutide 3 mg once daily significantly decreases AHI, body weight, systolic blood pressure, and hemoglobin A1c compared with placebo over 32 weeks. Liraglutide is generally well tolerated with transient mild-to-moderate adverse effects. The common adverse effects are gastrointestinal and include diarrhea, constipation, dyspepsia, vomiting, and nausea. The other adverse effects include headache, increase in pulse rate, nasopharyngitis, and increase in lipase.[62,72] Liraglutide is more effective in patients who refused or CPAP failures with moderate-to-severe OSA with adjunct to diet and exercise. So, weight reduction with liraglutide is one of new treatment options for OSA patients; however, further studies are require for the duration of treatment and long-term benefit of this drug.

Hypoglossal Nerve Stimulation

The loss of genioglossus muscle activity during sleep leads to upper airway obstruction in OSA patients. The direct electric stimulation of the genioglossus via intraoral, intramuscular, or submental electrodes is able to dilate the upper airway, and increase airflow, decrease AHI, but also induce sleep arousals and fragmentation.[74,75] To minimize the adverse events and to be a more effective method, a method of electric stimulation of the hypoglossal nerve is being implemented. The HNS electrically stimulates the hypoglossal nerve, a motor nerve innervating the protrusor, and retractor muscle of the tongue through eletrodes.[76-78] The electrode is made of platinum/iridium, with tripolar design that distributes the current uniformly and avoids nerve damage. The leads of the stimulating electrodes are tunneled via the neck to a neurostimulator placed subcutaneous in chest.[79,80] Studies have shown that there is significant improvement in symptoms of sleepiness, mood, quality of life, and reduction in AHI with HNS.[76,77,79,81,82] Various trials have shown that there is significant decrease in AHI with HNS and is maintained for more than 3 years after implantation.[76,77,81-84] The HNS is a US FDA-approved treatment option for patients with OSA, who are unable to use or not consistently benefiting from CPAP therapy. It has been shown that HNS had no therapeutic effect in high BMI patients.[77,79] The HNS is a surgically invasive procedure with few serious adverse events, such as infection at the site of procedure and malfunctioning of neurostimulator. The other minor adverse events are numbness, pain, swelling at incision site, and temporary tongue weakness.[76,77,79]

Nasal Expiratory Positive Airway Pressure

Increasing lung volume has beneficial effects in decreasing AHI. The CPAP therapy leads to increase in lung volume and further lung volume increase has an additive effect in reducing AHI.[85] Expiratory positive pressure has been investigated as a more practical means to increase end expiratory lung volume and thereby improve OSA. The highest risk of upper airway collapse occurs at the end of the expiratory phase because of a lack of positive pressure or phasic activation of the upper airways.[86] The nEPAP is a system that creates high resistance during expiration but not during inspiration through small mechanical valves placed with adhesives in each nostril.[87] Riaz et al[88] in a meta-analysis of 18 studies have shown that there was a 53.2% decrease in AHI and an improvement in the quality of life; however, nEPAP did not entirely eliminate OSA and adherence is still an issue like CPAP therapy. The nEPAP benefits more in patients who are intolerant of CPAP or are traveling. It is not a good

option for patients with hypercapnia respiratory failure, respiratory muscle weakness, bullous lung disease, and pneumothorax.[88,89]

Positional Therapy

It is a known fact that supine position doubles a patient's AHI compared with lateral position sleeping.[90] In a recent analysis, it is shown that 60% of patients were supine-predominant OSA.[91] In a drug-induced endoscopy study, it has been shown that the upper airway collapses at multiple levels in the supine position as compared with at a single level in the lateral position.[92] The various positional therapies include attaching a tennis ball to the neck, sleep hygiene, and night shift. Studies have shown that positional therapy significantly decreases AHI, but long-term compliance is still an issue.[7,54] Night shift is a recent device that consists of a small electronic monitor attached to the lower part of the neck before falling to sleep. When the patient changes position to the supine, the night shift begins to vibrate slowly and increases in intensity until a position change occurs.[93] It has been shown that there is greater reduction in AHI and improvement of sleep architecture with night shift compared with other types of positional therapy.[94,95] So, positional therapy is effective only in subset of OSA patients with positional OSA and also in combination with measures like oral appliance therapy and CPAP.

Pharmacologic Treatment for reducing Loop Gain/reducing Arousal and decreasing Surface Tension

Many pharmacological agents are tried in treatment of OSA; however, no single drug is approved for OSA treatment till date. In a recent Cochrane review, various drugs were assessed for treating OSA. These drugs are: Increasing ventilatory drive (like, acetazolamide, theophylline, and progestogens), increasing upper airway tone (like serotonergics and cholinergics), decreasing rapid eye movement (REM) sleep (like clonidine and antidepressants), increasing arousal threshold (like eszopiclone and zopiclone), and increasing the cross-sectional area or reducing the surface tension of the upper airway (like fluticasone and lubricant). This review concluded that there is some benefit with few drugs; however, their adverse events need to be considered. While there is no or little benefit with some drugs on AHI, even if they have effect on OSA, adverse effects are more than benefits.[96] The commonly used pharmacological agents for treatment of OSA or in clinical trial are the following:

Eszopiclone: A non-benzodiazepine sedative, used to increase arousal threshold without effecting genioglossus activity.[96] However, the studies have shown that there is increase in respiratory arousal threshold, but had no effect on AHI, and increased oxygen desaturation.[54,96,97]

Acetazolamide: It is a respiratory stimulant acting via inhibition of carbonic anhydrase inhibition. Carbonic anhydrase inhibitors are used to stabilize the ventilatory control system by a decrease in high loop gain. Studies have shown that acetazolamide decreased loop gain, decreased AHI in non-REM (NREM) sleep. There is a need for larger randomized study for further evaluation of this drug in OSA treatment.[98,99]

Dronabinol: Nonselective cannabinoid type 1 and type 2 receptor agonist. It significantly reduced AHI and improved subjective sleepiness and alertness.[100,101] Dronabinol most likely acts through increases in upper airway tone though inhibition of vagal nerve.[54,102] Minor adverse events of this drug are somnolence and increased appetite.[101] Further larger randomized studies will be needed to establish the safety and efficacy of dronabinol in the treatment of OSA.

Treatment Combinations and Phenotyping: Many OSA patients have more than one mechanism. Combination of two or more treatments might lead to greater decreases in AHI and greater improvements in OSA symptoms.[103,104] The combination of an oral appliance and positional therapy led to further significant decreases in AHI compared with single-agent treatments.[54,105] To correctly combine these treatment options, the patient will have to be specifically phenotyped via polysomnography to differentiate and specify the pathophysiology of OSA. There are published methods of OSA mechanism phenotyping according to patient's sleep position, ventilation parameters, loop gain, arousal threshold, and upper airway gain, and if apneic events occur in REM or NREM sleep.[92,106] The various treatment options according to pathophysiology of OSA with their advantages and disadvantages are summarized in Table 2.

CONCLUSION

The OSA is a heterogeneous disorder with different mechanisms that lead to collapse of upper airway. Rigorous evaluation to find out the exact mechanism or combination of mechanism seems to be most appropriate treatment. As phenotypic base treatment options are well tolerated and have more adherence, it leads to better long-term outcome. The various newer therapies that are now widely used are mandibular advancement device, pillar procedure, HNS, increasing expiratory volume, and positional device. Combination therapy with two or more devices may be useful in certain patients.

Table 2: Various newer treatment options with their advantages and disadvantages

Treatment	*Advantages*	*Disadvantages*
Mandibular advancement devices	Reduces extraluminal pressure at the oropharyngeal level Activates the upper airway musculature Better adherences than CPAP More effective in females, small neck size, low BMI, and retrognathic jaw	Overall less effective than CPAP Dental alterations: Pain, overbite, protrusion reduction Temporomandibular syndrome Myofascial pain Excessive salivation Dryness of oral mucous membrane
nEPAP	Greater adherence than CPAP Inexpensive Better for travelers Noninvasive	Poor adherence Not entirely eliminates OSA Not good option for patients with hypercapnic respiratory failure, pneumothorax, and bullous lung
Pillar	Minimal invasive More effective in OSA with palatal component More effective in mild-to-moderate OSA with low BMI	Discomfort with deglutition Ineffective with retropalatal obstruction Operative procedure Postoperative complications
Hypoglossal nerve stimulation	Only treatment that attempts to eliminate OSA Increases inspiratory airflow	Invasive procedure Not effective in high BMI patients May have secondary effects like: Paralysis of the phrenic nerve, muscle fatigue, changes in the type of muscle fiber, soft tissue abrasion, and hypertrophy of lingual musculature
Positional therapy	Shown to be the most effective for positional OSA Can be easily used in combination Noninvasive	Sleep disruption at the beginning of treatment
Liraglutide	More effective in obese Can be used in combination with other treatment	Injectable Gastrointestinal adverse effects Duration of treatment

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