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REVIEW ARTICLE

Recent advances in obstructive sleep apnea pathophysiology and treatment

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Abstract

Obstructive sleep apnea (OSA) is a sleep disorder characterized by recurring collapse of the pharyngeal airway leading to restricted airflow. OSA is becoming increasingly common with at least moderate disease now evident in 17% of middle aged men and 9% of women. The list of recognized adverse health consequences associated with OSA is growing and includes daytime symptoms of sleepiness, impaired cognition and risk of motor vehicle accidents as well as associations with hypertension, cardiovascular morbidity, malignancy and all-cause mortality. In this context adequate treatment of OSA is imperative; however, there are well-recognized pitfalls in the uptake and usage of the standard treatment modality, Continuous Positive Airway Pressure (CPAP). A broad range of pathophysiological mechanisms are now recognized beyond an anatomically smaller pharyngeal airway and impaired compensatory pharyngeal muscle responsiveness. Perturbations in ventilatory control stability, low arousal threshold, sleep-related decrease in lung volume and fluid redistribution as well as upper airway surface tension have all been shown to variously contribute to sleep-disordered breathing. Many new therapies are emerging from these advances in understanding of the mechanisms of OSA. Although many may not be universally effective, the promise of phenotyping patients according to their individual pathophysiology in order to target one or more therapies may prove highly effective and allow the treatment of OSA towards a personalized medicine approach.

Key words: Obstructive Sleep Apnea, pathophysiology, phenotyping, treatment.

INTRODUCTION

Obstructive sleep apnea (OSA) is an increasingly common sleep disorder, with moderate to severe disease now evident in 17% of men and 9% of women in the middle aged population.[1] OSA is characterized by intermittent periods of complete (apnea) or partial (hypopnea) upper airway obstruction, by definition lasting at least 10 s during sleep. This dysfunction of the upper airway results in disturbances to oxygenation, intrathoracic pressure swings and fragmented sleep, which in turn cause a cascade of inflammatory and cardiometabolic perturbations. Daytime symptoms of excessive daytime sleepiness and impaired neurocognitive function follow as well as broad range of long-term adverse health outcomes including increased risk of motor vehicle accidents,[2] reduced quality of life,[3] hypertension, cardiovascular morbidity, malignancy and all-cause mortality.[4–7] The mainstay of OSA treatment has been Continuous Positive Airway Pressure (CPAP) delivered by a mask interface to pneumatically splint open the airway to prevent collapse. Undoubtedly, CPAP

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is highly efficacious in reducing obstructive events; however, health benefits are dependent on usage for a large proportion of sleep time.[8] Many patients are unable to tolerate and initiate CPAP treatment and of those who do only around half use the device at the minimum recommended level (≥4 h/night).[9] Furthermore this drops off to 17% after 5 years[10] indicating long-term treatment of OSA by CPAP in the majority of people is suboptimal and reversal of adverse health risks unlikely in the real world.

However OSA is increasingly recognized as a heterogeneous disorder with multiple pathophysiological causes for which CPAP represents a "one size fits all" solution by preventing upper airway collapse. New concepts in OSA pathogenesis and phenotypes have recently emerged as well as novel treatments. Targeting OSA treatment to individual pathologies could broaden treatment options for the patient and improve patient acceptance and outcomes. Recent advances in understanding of OSA pathophysiology and novel treatments could help move towards a future of a personalized medicine approach to treatment of OSA where the primary underlying pathogenic mechanisms are targeted in treatment. In this review we discuss OSA pathophysiology related to anatomical and neuromuscular mechanisms, lung volume, ventilatory control, arousal threshold, upper airway surface tension and rostral fluid shift. We present a review of these different pathological mechanisms and recent treatment strategies targeted to each as well as highlight recent understanding in OSA phenotyping.

ANATOMICAL MECHANISMS

Obstructive sleep apnea patients tend to have smaller pharyngeal airways compared to non-OSA controls, with a narrower cross-sectional area of the airway lumen, which is more vulnerable to collapse.[11–13] This smaller pharyngeal airway space can be attributed to structures of the surrounding tissues including upper airway soft tissues, regional adipose tissue and the craniofacial skeleton. OSA patients have been shown to have bigger tongues, greater lateral pharyngeal wall width and longer soft palates than controls.[14] Obesity, as one of the major risk factors, is also likely to contribute to OSA through directly compromising pharyngeal airway space by adding to the surrounding tissue mass, particularly through enlargement of the parapharyngeal fat pads and fat deposited in the tongue.[14–16] It has long been recognized that craniofacial skeletal restriction is also a feature of OSA. Common findings such as narrow cranial base, smaller maxilla and mandibular retrognathia are all likely to encroach on upper airway soft tissues and result in a smaller airway space.[17] Studies during anesthesia with blunting of neuromuscular input confirm that sleep apneics have a more collapsible pharynx based on structural properties alone.[18] Collapsing pressure from surrounding pharyngeal tissues is generated by the interaction of pharyngeal soft tissues and the surrounding craniofacial skeletal enclosure.[19] Watanabe and colleagues proposed a conceptual "box" model of extraluminal pharyngeal tissue pressure as proportional to the amount of tissue within the bony "box" comprising the skeletal borders of the maxilla, mandible and cervical column.[19] In this model 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 size (as in obesity and/or oropharyngeal crowding) or by a normal amount of tissue compressed into a reduced enclosure (as in craniofacial abnormality). Imaging studies have demonstrated a larger tongue for a given maxillomandibular bony enclosure size in OSA compared to controls, supporting an "anatomical imbalance" as a contributing factor to OSA.[20] Indeed both mandibular advancement (effective enlargement of the bony enclosure) and weight loss (soft tissue reduction) reduce collapsibility of the passive pharynx.[21,22] Upper airway collapse resulting from "anatomical imbalance" may primarily be driven by either obesity or craniofacial factors, depending on the patient population.[23] Ethnicity and gender may influence obesity and craniofacial risk factors and their contribution to OSA.[24,25] For example, craniofacial skeletal restriction in Chinese but obesity in Caucasians is evident for the same degree of sleep apnea severity.[23]

Another anatomical mechanism in OSA is position dependency. It is well recognized that obstructive respiratory events occur more often and are often worse when the body is in the supine position. There are various definitions of positional OSA but at least a 50% greater Apnea–Hypopnea Index (AHI) in the supine compared to non-supine position is used and further there may be a requirement for AHI in the lateral posture to be in the normal to mild range (>5 or >10 events/h).[26] A supine-predominant form of OSA is estimated to occur in at least half of all OSA patients.[27] The upper airway is more collapsible in the supine compared to lateral position[28] and this may relate to effects of body position and gravity on airway geometry, upper

airway dilator muscle responsiveness and lung volume.[27] Lower levels of obesity appear to be associated with position-dependent OSA. There is a lower prevalence of positional OSA in overweight patients undergoing bariatric surgery[29] and weight gain appears to change positional-dependent OSA patients to non-positional over time.[30] Positional OSA patients appear to have certain craniofacial features such as a more retropositioned mandible,[31] which may contribute to greater airway collapse while in the supine position. Although the association of supine position and severity of OSA and snoring has long been recognized, it has recently been demonstrated that there is significant night-to-night variability in the position dependence of an individual's sleep-disordered breathing.[32] However, a proportion of males with a supine to nonsupine OSA ratio of 4:1 may still represent a distinct phenotype of position-dependent OSA.[32]

TARGETED ANATOMICAL THERAPEUTIC APPROACHES

Treatment approaches to increase the size and patency of the upper airway are commonly employed to treat OSA. Mandibular advancement devices, which hold the jaw in a forward position during sleep, are often preferred to CPAP and provide a clinical response in around two-thirds of patients.[33] Mandibular advancement increases the size of the upper airway space and decreases extraluminal tissue pressure.[34,35] Weight loss is also a treatment strategy that improves the severity of OSA.[36] Weight loss reduces the collapsibility of the upper airway,[21] which may partially occur through an increase in pharyngeal airway size secondary to reduction in local fat deposits such as in the pharyngeal fat pads.[15,37] Various surgical interventions are also used in the treatment of OSA and targeted at multiple levels of the upper airway and different tissue structures.[38] Removal of excess pharyngeal soft tissues such as in uvulopalatopharyngoplasty (UPPP) and tonsillectomy has traditionally been most widely used, although impact on OSA can be modest.[39] Remodeling of the pharyngeal tissue properties using radiofrequency thermotherapy to reduce tongue volume and palatal implants may also be beneficial in some patients.[39,40] Maxillo-mandibular advancement (MMA) to increase the size of the craniofacial enclosure is a much more invasive procedure but appears to be most successful of the surgeries in terms of reducing AHI.[41] Although surgery may be an ongoing and attractive treatment option for some patients, more work is needed to build the evidence base around different surgeries and patient selection.

Treatment of positional OSA is aimed at avoidance of the supine posture during sleep. This is most simply achieved using the "Tennis Ball technique", which involves a ball or similarly protrusive object secured to the patient's back which will prevent supine sleep as discomfort will cause the patient to resume the lateral position. A reduction in supine sleep time when using such supine avoidance devices has been confirmed[42,43] as well as reductions in AHI and 24 h blood pressure.[44] Comparison of positional devices to CPAP in terms of a single night treatment effects have shown that positional therapy is highly effective;[45] however, long-term compliance may be suboptimal with some positional devices.[46] Further long-term studies on the role of positional therapy are required.[26]

NEUROMUSCULAR MECHANISMS

Upper airway patency is maintained by activity of the pharyngeal dilator muscles. Stabilization of the airway by pharyngeal muscle tone, of which the genioglossus is the largest and best studied, is particularly important in those with an already anatomically compromised airway.[47] Upper airway dilator muscle activity is regulated by inputs from mechano- and chemo-receptor feedback, output from the brainstem central respiratory pattern generator and furthermore is influenced by sleep and wake states.[48–51] Therefore control of the pharyngeal muscles can be variously affected by local negative pressure stimuli, respiration and the onset of sleep.

Genioglossus muscle activation is negatively correlated with upper airway collapsibility and pharyngeal resistance.[52] OSA patients have increased dilator muscle activity compared to matched controls during wakefulness,[53] suggesting a neuromuscular compensatory mechanism exists to counteract collapsing forces related to an anatomically small airway. However at the onset of sleep, dilator muscle activity is reduced and this drop is more pronounced in OSA patients than controls.[54,55] Reduced muscle stimulation appears to occur due to a loss of this greater "wakefulness" stimulus in OSA patients.[56] A general loss of neuromuscular compensation therefore appears to contribute to propensity to pharyngeal collapse during sleep. Protective reflexes in response to local pressure perturbations, elicited via mechanoreceptors in the pharynx, also serve to increase motor output from the hypoglossal nerve. This 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 compared to controls in the awake state.[57] However the reflex is known to decrease from the wake to non-rapid eye movement (NREM) to rapid eye movement (REM) sleep states,[58–61] and OSA patients have reduced neuromuscular compensation in response to pharyngeal obstruction during sleep compared to controls.[62] Disturbances in upper airway dilator muscle control are clearly a pathogenic mechanism underlying OSA.

TARGETED NEUROMUSCLAR THERAPEUTIC APPROACHES

Nocturnal activation of lingual muscles by hypoglossal nerve stimulation (HNS) has been investigated as a means to overcome the sleep-related decrease in pharyngeal dilator muscle tone to maintain a patent airway. Stimulation of genioglossus motor activity has been shown to improve airflow in a dose-dependent manner and decrease pharyngeal collapsibility during sleep.[63–66] Activation of the tongue through transcutaneous or direct intra-muscular means has limitations for treatment and direct stimulation of the hypoglossal nerve is preferable as a purely motor response is elicited without potential associated sensory stimulation to cause arousal from sleep.[67] HNS to activate the lingual muscles is now available via implantable devices with feasibility and efficacy data reported to one year follow-up. These devices consist of a pulse generator implanted in the chest wall with an electrical lead extending unilaterally to an electrode cuff, which wraps around the hypoglossal nerve. Some systems incorporate an additional sensing lead in order to gate stimulation to inspiration,[68–70] while alternatively a continuous stimulation system with rotation of electrode stimulation within the cuff in order to avoid nerve fiber fatigue.[71]

Generally initial trials have found around a 50% reduction in AHI, sustained at 12 months after implantation, and associated improvements in subjective daytime sleepiness and quality of life.[68–72] Compliance data show that the device is used an average of 89% of nights for nearly 6 h for 6 months, which was relatively stable at 12 months[68,72] and there is some evidence that a sustained effect of HNS stimulation on reduction of obstructive events may remain when the device is not in use.[73] How long the effect is sustained for is not yet clear but potentially it may not be necessary to apply nightly stimulation for adequate treatment. Although a randomized withdrawal study after 12 months of treatment, found that treatment responders assigned to not using their device for a 7-day period showed an increase in AHI back to near baseline levels.[70] Endoscopic and fluoroscopic imaging of the pharynx during HNS show anterior movement of the tongue base and hyoid bone in most patients and widening of the anteroposterior airway in response to stimulation.[71,74] Appropriate patient selection for this form of treatment is somewhat unclear with initial studies including patients with at least moderate OSA, a BMI less than 40 kg/m^2 and predominantly CPAP failures. Potential predictors of response include lower BMI, less severe OSA and pattern of retropalatal airway collapse during drug-induced sleep endoscopy.[69] Therefore feasibility trials are promising and further work to select appropriate patients may further improve outcomes and support HNS as a treatment option in a proportion of OSA patients.

Awake upper airway muscle training has also been suggested to have a positive influence on reducing upper airway collapse during sleep. A randomized controlled study of didgeridoo playing showed a reduction in AHI and improvement in OSA symptoms.[75] This concept has further been investigated in using a set isometric and isotonic oropharyneal exercises to target the tongue, soft palate and lateral pharyngeal wall muscles using stomatognathic functions of suction, swallowing, chewing, breathing and speech.[76] In a small randomized controlled study of 3 months of 30 min daily oropharyngeal exercise OSA, moderate OSA patients with good adherence (>85% of exercises completed) showed a nearly 50% reduction in AHI with 65% shifted into the mild OSA category.[76] A decreased neck circumference, correlating with AHI reduction, was noted in the exercise group, suggesting a direct effect on the upper airway structures. Although training the muscles whose deficiency contribute to upper airway collapses seems to have some benefit in initial investigations, there is still more to be understood in terms of an ongoing therapy. It is unknown if effects are sustained and precisely which exercises provide most benefit and also the frequency with which they should be applied to help streamline the therapy. However, in patients who are motivated, oropharygeal exercises may prove to be an option in mild disease or perhaps reduce the level of other treatments, such as CPAP pressure.

Increasing upper airway muscle tone using pharmacological agents has also been considered in the treatment of OSA. A range of drugs have been trialed primarily targeting the serotonergic and cholinergic

systems based effects on upper airway muscle tone in animal studies.[77] Trials are relatively limited, although drugs proposed to act on upper airway tone have reported some improvements on OSA indices in some trials.[77,78]

ROLE OF LUNG VOLUME

Lung volume also has an influence on upper airway structure and function. Lung volumes fall with sleep and the recombinant position.[79] In both OSA and healthy controls and across both the sleep and wake states, increased lung volume improves upper airway patency, reduces collapsibility and airflow resistance and increases pharyngeal cross-sectional area.[80–86] Furthermore increased lung volume in OSA patients reduces therapeutic CPAP pressure requirement.[81] Therefore reduced lung volumes negatively impact on airway patency and contribute to sleep disordered breathing.

Lung volume effects on the upper airway may primarily be mediated by mechanical effects that provide caudal traction and lead to stiffening of upper airway structures. Tracheal traction via mechanical linkage to mediastinal structures in response to increasing lung volume and intra-thoracic pressure improves upper airway patency and resistance.[87,88] The effect is independent of upper airway muscle activity and is lost upon severing of caudal thoracic structures in anesthetized dogs.[87] Increased lung volume 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.[89–91]

Obesity is the strongest known risk factor for OSA, with OSA attributable to excess weight and obesity in more than half of adults.[92] Obesity reduces lung volume, particularly in the supine position[93] and is associated with increased fat deposition in the chest wall.[94] It has been shown that obese OSA patients have a greater reduction in end expiratory lung volume and diaphragm activity at sleep onset compared to healthy controls.[95] Obese OSA patients have a smaller pharyngeal cross-sectional area, which is more sensitive to lung volume changes compared to obesity-matched controls,[85] suggesting there may be some difference in obesity distribution or influence in OSA patients. Reduced lung volume secondary to obesity may contribute to increased propensity of upper airway collapse. Weight loss induced changes in lung volume may be an important in reducing pharyngeal collapse as regional fat loss and upper airway volume alone does not explain the improvement in OSA.[37]

TARGETED THERAPEUTIC APPROACH TO INCREASING LUNG VOLUME

Increasing lung volume has beneficial treatment effects in reducing AHI and therapeutic CPAP pressure requirement.[81,96] CPAP itself increases lung volume and further lung volume increase has an additive effect in reducing AHI.[96] However, viability of further therapeutic manipulation of lung volume is unclear. Expiratory positive pressure has been investigated as a more practical means to increase end expiratory lung volume and thereby improve OSA. 10 cm H_20 expiratory positive pressure delivered through mask interface was found to result in a less than 20 mL increase in end-expiratory lung volume and a change in respiratory patterns but not AHI.[97] A disposable device to increase expiratory positive pressure through a valve delivering minimal inspiratory and high expiratory resistance sealed to each nostril has been tested.[98] A 3-month randomized sham-controlled study of 127 OSA patients on the EPAP device showed around a 40% decrease in AHI and improvement in subjective daytime sleepiness.[98] Treatment success (>50% AHI reduction or treatment AHI<10/h) was evident in double the number of patients on active compared to sham device (60% vs 30%) with self-report compliance of 88% on nights.[98] In successfully treated patients showing good compliance (>4 h/night, $n = 41$), reduced AHI was maintained at 12 months in the 83% still on treatment.[99] The mechanisms of this disposable nasal device have been investigated using magnetic resonance imaging of the upper airway and lung with and without application of expiratory positive pressure during wakefulness, of 4–17 cm H_2O.[100] The expiratory positive pressure device resulted in a 46% increase in functional residual capacity, suggesting involvement of tracheal traction secondary to increased lung volume in reducing upper airway collapse. There was a trend for upper airway cross-sectional area to increase at end expiration, suggesting additional dilation of the airway may contribute towards reducing collapse, although this did not reach significance. Additionally, hypoventilation and rise in P_{CO2} with device use was also observed suggesting there may be alterations to upper airway function through respiratory drive. These findings suggest expiratory positive pressure may improve OSA through effects on lung volume, although this has not been confirmed during sleep. Lung volume also increases with weight

loss in the morbidly obese.[101] Weight loss improves OSA[102] and one potential mechanism for improvement in upper airway stability is an increase in lung volume secondary to weight loss. Increased lung volume may also improve respiratory control stability by improved blood gas exchange.

VENTILATORY CONTROL MECHANISMS

Although anatomical compromise and deficiencies in recruitment of compensatory pharyngeal muscles are key factors in promotion of upper airway collapse, the ventilatory control system also plays a role in the development of obstructive breathing.[103] Neuronal output from the central respiratory pattern generator controls breathing to maintain optimal levels of oxygen and CO_2; however, instability in control of this system can lead to periods of cyclic breathing and an obstructed airway.[104] It has been well documented that there is greater instability of the ventilatory control system in OSA.[104–108] Decreased airway resistance and increased airflow as occurs following termination of apnea with arousal can lead to hyperventilation, which promotes central apnea and hypopnea.[109] This low respiratory drive and subsequent hypocapnia inhibit activity of the respiratory pump muscles (diaphragm and upper airway dilators) and therefore predispose the upper airway to collapse and obstruction and then further arousals.[110,111] The chemoreceptor control system therefore plays an important role in determining whether obstructive events are followed by unstable breathing, which further exacerbates the problem.[103]

Ventilatory instability has been described in terms of "loop gain" an engineering concept which describes the stability of a negative feedback control system in terms of the ratio of the response of the system to a given disturbance.[112,113] Important components of loop gain in control of breathing are chemoresponsiveness of the system (controller gain) and efficiency of CO_2 excretion (plant gain). High loop gain reflects an excessive reaction to a disturbance which ultimately leads to instability and fluctuations of hyper and hypoventilation.[104] Conversely low loop gain reflects a more controlled response to perturbation and ultimately more stable breathing.

There is variability in the contribution of stability of ventilator control to OSA between patients[109] and it has been shown that strongest correlation between loop gain and AHI occurs in those with a relatively less collapsible airway.[107] Although there may be individual differences in the predominance of this mechanism, instability of ventilatory control, or high loop gain, is an important pathological contributor to OSA.

TARGETED VENTILATORY CONTROL THERAPEUTIC APPROACHES

Oxygen and pharmacological therapy targeted at stabilizing the ventilator control system have been considered. Oxygen helps stabilizing ventilation by reducing peripheral chempresponsiveness and has been tested against room air in OSA patients with and without known ventilatory control instability (high and low loop gain, respectively) during overnight polysomnography.[112] Oxygen resulted in a reduction in loop gain and halved the AHI in those with high loop gain but had minimal effects on sleep disordered breathing in the low loop gain group. Acetazolamide (a respiratory stimulant via metabolic acidosis) has also been trialed for its effects on loop gain.[114] In 13 OSA patients one week of drug administration resulted in an approximately 40% reduction in loop gain and halved the AHI. There were no overt effects on other pathological determinants of OSA such as pharyngeal collapsibility or muscle responsiveness. These studies suggest that manipulating loop gain in patients with unstable ventilator control may lead to improvement in OSA. In terms of health outcomes, a recent study of 12 weeks of CPAP versus nocturnal supplemental oxygen on markers of cardiovascular risk found only CPAP to have an effect on reducing blood pressure parameters.[115]

ROLE OF AROUSAL THRESHOLD

Obstructive respiratory events are generally terminated by a cortical arousal from sleep leading to airway opening. Therefore arousals have been considered a protective event, which terminates apnea and resumes airflow. However, a respiratory event can be terminated without involving an arousal[116] and other neuromuscular and respiratory compensatory mechanisms can increase dilator muscle activity in response to obstruction and open the airway.[117] 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.[111,116] CO_2 levels may be driven below the apnea threshold[104] and reduce upper airway dilator muscle activation leading to further airway collapse.[48,118–120] In OSA patients with a low arousal

threshold (awaken easily in response to airway obstruction) 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.[103]

TARGETED THERAPEUTIC APPROACH TO RAISING AROUSAL THRESHOLD

Preventing arousal associated with the onset of airway obstruction in order to allow activation of other compensatory mechanisms to open the airway may be of benefit in those with a low arousal threshold.[120,121] Increasing the arousal threshold by pharmacological means using sedatives has been investigated as a treatment for OSA. However, to be an appropriate treatment, it is necessary that sedatives should not also impair upper airway muscle activity.[122–124] Eszopliclone, a non-benzodiazepine sedative, has been tested for effects on arousal threshold and OSA severity.[125] 17 OSA patients without significant hypoxemia and a predetermined arousal threshold attended for two nights of polysomnography with administration of either a placebo tablet or 3 mg eszopliclone. Results showed that eszopliclone was associated with an overall increase in the arousal threshold and reduction in AHI associated (23%) with increased sleep duration and quality. The improvement in AHI was specific to eight patients defined as having a low arousal threshold at baseline, which was just over a 40% reduction in this group. These findings suggest that appropriate sedatives may be at least a useful therapeutic adjunct in selected OSA patients with a low arousal threshold and the ability to adequately recruit pharyngeal muscles.

ROLE OF SURFACE TENSION

Adhesive forces between the mucosal surfaces of the upper airway contribute to collapse and high surface tension further opposes re-opening of the upper airway following closure. The pressure required to open and close the upper airway has been shown to relate to surface tension of the upper airway lining liquid in anesthetized rabbits and humans.[126,127] Reducing surface tension using an exogenous surfactant improves upper airway patency[128] and improved closing pressures of almost 2 cm H_2O has been demonstrated.[128] It has been shown that upper airway lining liquid has a higher surface tension in OSA patients compared to healthy controls although salivary flow rates did not differ.[129] Therefore surface tension of the upper airway mucosa may facilitate or protect the upper airway from collapse in individuals.[130]

TARGETED THERAPEUTIC APPROACH TO LOWERING SURFACE TENSION

Manipulation of surface tension of the upper airway lining liquid may represent a therapeutic mechanism to improve and help maintain airway patency. Alteration of upper airway surface tension may be achieved through application of surfactant and modification of breathing route and salivary flow.[131] Application of exogenous topical surfactants to the upper airway have shown a reduction in AHI in the order of 20–40%.[128,132,133] The effect on obstructive respiratory events is primarily in reduction of hypopneas, rather than apneas.[128,134] Nasal breathing has been shown to increase oral mucosal wetness and decrease the surface tension of upper airway liquid lining, whereas the oral breathing route has the opposite effect.[135] Surfactant therapy and/or alteration of the breathing route and mucosal properties may therefore represent means to lower upper airway surface tension and reduce OSA severity.

ROLE OF ROSTRAL FLUID SHIFT

A role of nocturnal rostral fluid shift in the pathogenesis of sleep apnea has emerged from the observation of high OSA prevalence in patients with fluid retaining states such as heart and renal failure.[136–138] The concept is that during the day, when people are predominantly in an upright position, gravity causes fluid to pool in the legs. At night upon reverting to the supine position, gravity then acts to move the accumulated leg fluid rostrally and subsequently increased fluid volume in the neck region increases tissue pressure and collapsibility of the pharyngeal airway.

In healthy subjects it has been demonstrated that application of lower body positive pressure results in an increase in neck circumference and the pharyngeal airway itself shows a decrease in cross-sectional area, increases in resistance and overall increase in collapsibility.[139–141] Increase in pharyngeal resistance in response to lower body positive pressure has been shown to be greater in OSA patients than controls for equivalent fluid volume shifts.[142] It has further been shown that the volume of fluid shifting overnight from the legs to the neck is strongly correlated with AHI in nonobese OSA males[143] as well as in those with fluid

retaining conditions of heart failure,[144] end-stage renal disease[145] and drug-resistant hypertension.[146,147]

Interestingly there appear to be differences in the effect of fluid shift on OSA between men and women. In heart failure patients, women showed a lesser increase in neck circumference for an equivalent reduction in leg fluid and there was no correlation between changes in fluid volume and AHI.[148] In healthy men and women the effect of lower body positive pressure on upper airway collapsibility is much greater in men than women.[149] This suggestion of different patterns of rostral fluid movement between men and women may be one mechanism that explains the gender difference in OSA prevalence.

TARGETED THERAPEUTIC APPROACH FOR DECREASING FLUID VOLUME

If fluid accumulation in the neck region is contributing to pharyngeal collapsibility then reducing nocturnal fluid shifts could improve OSA. In non-obese OSA men volume of fluid shifting from legs correlated with time spent sitting during the day[143] and therefore increased activity may help reduce the volume of fluid available to shift. Although this has not been specifically assessed, exercise has been shown to improve OSA without weight loss.[150] Compression stockings, worn to counteract fluid accumulation in the legs during the day, have been shown to reduce AHI in the range of 30% in non-obese sedentary men with OSA with associated reductions in leg fluid volume and neck circumference changes.[151,152] A small uncontrolled study in hypertensive moderate-severe OSA patients of intensified diuretic therapy for 2 weeks showed an average 15% reduction in AHI with this reduction strongly correlated with leg fluid volume changes.[153]

PATHOPHYSIOLOGICAL PHENOTYPES OF OSA

Although a range of contributing pathogenic mechanisms towards OSA have been identified, this does not necessarily address the relative importance of each. A recent study by Eckert and colleagues[154] has attempted to define pathophysiological phenotypes of OSA by measuring four key anatomical and non-anatomical mechanisms within individuals with OSA. Anatomical collapsibility of the upper airway (measured by passive critical closing pressure, Pcrit) was assessed in conjunction with non-anatomical factors of arousal threshold, loop gain and upper airway dilator muscle responsiveness in more than 50 people with OSA. Analysis showed that 81% of patients had a significant anatomical vulnerability in terms of a highly collapsible airway. In terms of non-anatomic traits 36% showed minimal genioglossus muscle responsiveness, 37% had a low arousal threshold and 36% had high loop gain. At least one non-anatomic factor was evident in 69% of patients with multiple traits in 28% of these. Therefore, although a more collapsible airway appears to be a prime predisposing factor in the majority of OSA patients, other non-anatomic factors are important and are more so in some patients. For example, a sizable portion (19%) of patients did not display overt anatomical vulnerability (normal Pcrit) but had much higher loop gain values. This study identifies a method of ascertaining the contribution of four key OSA pathophysiologies in individual patients. Better understanding and quantification of these specific traits could lead to targeted treatment strategies (Table 1). Potentially lower success rates of some previously trialed treatment strategies may be partially due to inappropriate selection of patients with the wrong primary phenotype for that therapy. Therefore OSA phenotyping is likely to be an important part of future treatment pathways.

MULTIMODALITY THERAPY

Secondary to understanding underlying pathophysiological phenotypes of OSA is the potential to combine different therapies simultaneously to achieve the best outcome by targeting multiple pathogenic mechanisms. Eckert and colleagues[154] devised a scale to classify patients based on underlying pathological mechanisms of P_{crit}, Arousal threshold, Loop gain and Muscle responsiveness. Of those with a very collapsible airway (high P_{crit}), more than half also displayed at least one nonantomic trait (Arousal threshold, Loop gain, Muscle responsiveness) which could contribute to sleep-disordered breathing. In patients who only showed nonanatomic vulnerability there was still evidence of more than one contributing trait potentially in more than half of these patients. Two-thirds of patients with a moderately collapsible airway again also displayed non-anatomical traits. Therefore many OSA patients have more than one pathophysiological mechanism that could be targeted for therapy and therefore combination therapy may be a useful approach to treatment. With this approach, even if individual treatments do not completely resolve OSA, the combination of a few may address different pathological mechanisms and in

Table 1 Summary of potential treatment strategies for known mechanisms of obstructive sleep apnea (OSA)

Pathophysiological mechanism	Etiology	Proposed treatment options
Anatomical	Craniofacial skeletal restriction, enlarged upper airway soft tissues, obesity and upper airway adipose tissue deposition	Mandibular advancement splint, weight loss, upper airway and craniofacial surgeries, positional therapy
Neuromuscular	Sleep related decreases in upper airway dilator muscle tone and reflexes	Hypoglossal nerve stimulation, oropharyngeal muscle training, *pharmacological agents?*
Lung volume	Obesity, supine position	Expiratory positive pressure, weight loss
Ventilatory control	Instability of ventilator control system (high loop gain)	Oxygen therapy, acetazolamide
Low arousal threshold	Awakening in response to obstructive events before activation of dilator muscles occurs	Selected sedatives (eszopliclone)
Surface tension	High surface tension of upper airway liquid lining	Surfactant, restricting oral breathing
Rostral fluid shift	Fluid retention (e.g. heart and renal failure)	Diuretics, compression stockings, exercise?

combination produce a sufficient reduction in OSA. Therefore different combinations of positional devices, mandibular advancement splints, weight loss, oxygen and pharmaceuticals may produce a satisfactory treatment outcome. For example, the combination of mandibular advancement and genioglossus stimulation improves upper airway collapsibility (lowers P_{crit}) compared to either condition separately.[155] Upper airway surgery (UPPP) has been shown to be most successful in reducing lateral AHI but with minimal effects on supine AHI.[156,157] Therefore combination of surgery with positional therapy may also be of benefit. CPAP pressure requirement lower in lateral position[158] and therefore positional therapy in combination with CPAP may have some beneficial effects. Additionally combining treatments to counteract anatomical compromise (e.g. Mandibular advancement splint) and non-anatomic pathologies (e.g. Oxygen or acetazolamide to alter chemoresponsiveness) may be adequate therapy in selected patients.[109,154] Also weight loss is likely a useful adjunct to many therapies. A recent trial assigned obese moderate-to-severe OSA patients to either weight loss or CPAP or both and found the combination therapy to show better outcomes than CPAP alone in improvements in insulin sensitivity, dyslipidaemia and blood pressure parameters.[159]

CONCLUSION

Obstructive sleep apnea is a significant public health problem with increasing prevalence along with aging populations and rising obesity levels. It is increasingly appreciated that OSA is a heterogeneous disorder and multiple pathophysiologic causes are now recognized. Upper airway anatomy and collapsibility remains a fundamentally important pathophysiological factor. However non-anatomical factors, such as impaired muscle responsiveness, low arousal threshold, high loop gain, rostral fluid shifts, lung volume, additionally play a variable role. There are now a number of different treatment options to address OSA with variable treatment effectiveness. Patient phenotyping of OSA pathophysiology is therefore likely to inform treatment decisions and improve treatment outcomes in the future as we move toward realizing the promise of personalized medicine.

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