Obstructive Sleep Apnoea: Focus on Pathophysiology

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Abstract

Obstructive sleep apnoea (OSA) is characterized by recurring episodes of upper airway obstruction during sleep and the fundamental abnormality reflects the inability of the upper airway dilating muscles to withstand the negative forces generated within the upper airway during inspiration. Factors that result in narrowing of the oropharynx such as abnormal craniofacial anatomy, soft tissue accumulation in the neck, and rostral fluid shift in the recumbent position increase the collapsing forces within the airway. The counteracting forces of upper airway dilating muscles, especially the genioglossus, are negatively influenced by sleep onset, inadequacy of the genioglossus responsiveness, ventilatory instability, especially post arousal, and loop gain. Recent reports indicate that multiple endotypes reflecting OSA pathophysiology are present in individual patients. A detailed understanding of the complex pathophysiology of OSA encourages the development of therapies targeted at these pathophysiological endotypes and facilitates a move towards precision medicine as a potential alternative to continuous positive airway pressure therapy in selected patients.

Keywords

Obstructive sleep apnoea · Pathophysiology · Upper airway anatomy · Ventilatory control · Arousal · Endotype · Treatment

3.1 Introduction

Obstructive sleep apnoea (OSA) is characterized by recurring episodes of upper airway obstruction during sleep, leading to markedly reduced (hypopnoea) or absent (apnoea) airflow at the nose/mouth. The condition is usually associated with loud snoring and intermittent hypoxaemia, and apnoeas are typically terminated by brief micro-arousals, which result in sleep fragmentation and diminished amounts of slow wave sleep (SWS) and rapid-eye-movement (REM) sleep (Deegan & Mcnicholas, 1995). Patients with OSA are usually unaware of this sleep disturbance, but the changes in sleep architecture contribute significantly to the prominent symptoms of unrefreshing sleep and excessive daytime sleepiness (EDS) typically reported by many of these patients (Lévy et al., 2015). Furthermore, the intermittent hypoxaemia and sleep fragmentation associated with OSA generate cell and molecular responses that generate systemic

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inflammation, sympathetic excitation, and other responses that predispose to comorbidities, especially cardiometabolic and neuropsychiatric (McNicholas, 2019).

While the detailed pathophysiology of OSA is complex, the fundamental abnormality reflects the inability of the upper airway dilating muscles to withstand the negative forces generated within the upper airway during inspiration. In the normal setting, upper airway dilating muscles contract in a coordinated manner that is timed with each inspiration, thus counteracting the negative pressures that are generated within the upper airway during inspiration. Factors that increase these negative pressures or diminish the efficacy of dilating muscle contraction upset this balance and thus predispose to upper airway obstruction (Deegan & Mcnicholas, 1995). Any factor that results in narrowing of the upper airway will increase upper airway negative pressures during inspiration, thus promoting collapse (Fig. 3.1).

The present review explores the various factors contributing to an imbalance of forces within the upper airway that predispose to obstruction, discusses the mechanisms by which obstruction occurs, reviews the more recent evidence regarding pathophysiological endotypes and phenotypes that may help predict the development of OSA, and, finally, reviews the emerging role of targeted therapy for OSA based on individual pathophysiological mechanisms.

3.2 Pharyngeal Pressure

The most important factor contributing to increased negative pharyngeal pressure during inspiration is narrowing of the oropharyngeal airway, which results in increased upper airway resistance during inspiration (Lévy et al., 2015). There are many potential causes of such narrowing, which include structural narrowing because of craniofacial bony morphology, soft tissue accumulation in and around the oropharynx because of factors such as obesity or adenotonsillar hypertrophy, and transient factors such as fluid accumulation that gravitates towards the neck in the recumbent position.

3.2.1 Craniofacial Morphology

Most patients with OSA demonstrate a narrowed oropharyngeal airway that can be clinically assessed by the Mallampati score, which is graded 1–4 depending on the degree of narrowing (McNicholas, 2008a). The typical patient with OSA has a score of 3 or 4 (Yu & Rosen, 2020). There is increasing evidence that genetic

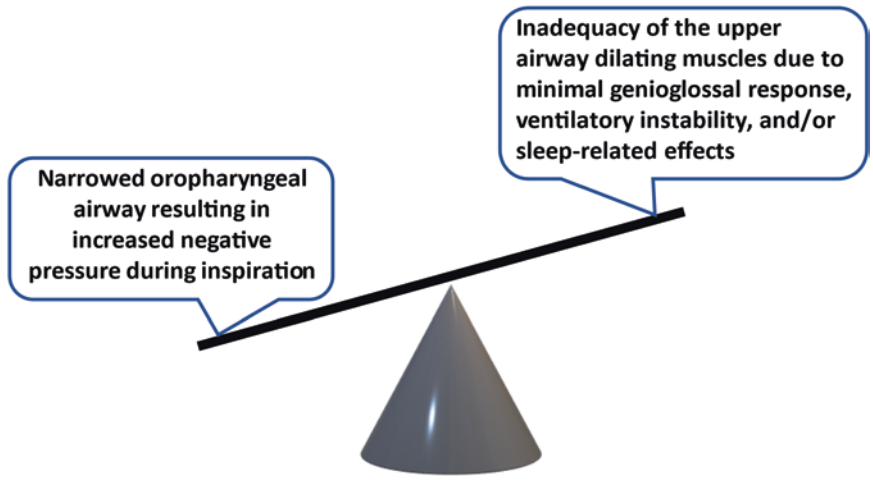

Fig. 3.1 Balance of forces affecting the patency of the upper airway with factors resulting in increased negative intrapharyngeal pressure and factors that reduce dilating muscle contraction promoting airway collapse

factors play a major role in this anatomical narrowing and, thus, are present from birth (Chen et al., 2018; Chi et al., 2014). Cephalometric and computed tomographic (CT) studies of the head and neck have demonstrated bony dimensions in the lower face and neck that result in narrowing of the upper airway (Neelapu et al., 2017; Sakat et al., 2016) (Abramson et al., 2010), and clinical assessment demonstrates micro/retrognathia in many of these patients (McNicholas, 2008a). On lateral cephalometry studies, OSA patients have a variety of anatomical abnormalities, including an abnormally small airway below the base of the tongue, a long bulky soft palate, an inferiorly placed hyoid bone and retrognathia (Rivlin et al., 1984).

Children with the Robin sequence (Bravo et al., 2005) or Treacher-Collins syndrome (Moraleda-Cibrián et al., 2014) are especially prone to OSA because of bony changes to the lower face and/or mandible that result in structural narrowing of the oropharyngeal airway (Tan et al., 2016). Micrognathia, which is the central feature of the Robin sequence, is particularly associated with OSA, as a small and/or retropositioned mandible places the base of the tongue closer to the posterior pharyngeal wall and interferes with the efficiency of the genioglossus muscle in keeping the tongue out of the narrowed pharynx (Sher, 1992). Indeed, the important role of such factors in this context is demonstrated by a case report from our department of a young girl with the Robin sequence who presented at the age of 12 with severe OSA complicated by right heart dysfunction and was successfully treated with nasal continuous airway pressure (CPAP) but resolved the OSA following growth of the mandible during puberty to the extent that CPAP therapy was no longer necessary (Kiely et al., 1998).

3.2.2 Soft Tissue Accumulation

Soft tissue accumulation in and around the upper airway can predispose to OSA by narrowing the oropharyngeal lumen. The two major entities in this context are obesity and adenotonsillar hypertrophy.

Obesity is closely linked to OSA and the role of central obesity in the pathophysiology of OSA occurs at different levels. The accumulation of fat in the neck results in oropharyngeal narrowing, which increases the collapsibility of the upper airway, and abdominal obesity reduces traction on the upper airway, which further predisposes to increased collapsibility (Deegan & Mcnicholas, 1995). 70% of patients with OSA are obese (Tuomilehto et al., 2013), and conversely, 50% of patients with a body mass index over 40 have an AHI over 10 (Resta et al., 2001). A higher body mass index (BMI) typically results in more severe OSA, especially in males and in younger subjects.

Adenotonsillar hypertrophy is associated with increased soft tissue within the oropharyngeal airway, which reduces the cross-sectional area and increases oropharyngeal collapsibility. Adenotonsillar hypertrophy is an important contributing factor in paediatric OSA, often in association with obesity (Dayyat et al., 2009). This form of OSA is amenable to surgical treatment by tonsillectomy (Stradling et al., 1990), although surgery may not be curative if there is co-existing obesity and/or an otherwise narrowed upper airway (Dayyat et al., 2009).

Infiltration of the upper airway soft tissues can reduce the upper airway lumen, as occurs in myxoedema, acromegaly, involvement by neoplastic processes, and mucopolysaccharidoses, and all such disorders have been associated with a predisposition to OSA (Grunstein et al., 1991; Orr et al., 1981).

3.2.3 Fluid Accumulation

Fluid accumulation, as occurs in patients with congestive heart failure, predisposes to OSA by the gravitational behaviour of oedema. Nocturnal redistribution of fluid in the recumbent position to dependent areas of the body such as the parapharyngeal soft tissues increases upper airway resistance and collapsibility (White & Bradley, 2013). Dietary sodium intake has been reported

to be closely correlated with the severity of OSA in patients with heart failure, likely as a consequence of fluid retention and redistribution (Kasai et al., 2011). Furthermore, non-obese male subjects with venous insufficiency who wore compression stockings during the day to limit fluid accumulation had a reduction in AHI of 36% when compared to those not wearing stockings (Redolfi et al., 2011). While these observations imply that diuretic therapy to remove excess fluid should benefit OSA, a randomized controlled trial of patients with severe OSA reported that sodium restriction and diuretic therapy resulted in only a modest improvement in AHI, implying that fluid accumulation only partially explains the aetiology of OSA in patients with heart failure (Fiori et al., 2018).

In patients with end-stage renal failure, fluid accumulation with associated nocturnal redistribution in the recumbent position results in oropharyngeal narrowing, like heart failure, which predisposes to OSA. In a group of 40 patients with end-stage renal failure on haemodialysis, 70% had an AHI >15, and these patients had a greater total body extracellular fluid volume, including neck, thorax and leg volumes despite no difference in BMI compared to those with an AHI <5 (Lyons et al., 2017). Furthermore, excess fluid removal by dialysis has been demonstrated to reduce the severity of OSA. One report indicated that removal of 2.2 L of fluid during a single ultrafiltration session resulted in a 36% fall in AHI, which also correlated with the volume of fluid removed (Lyons et al., 2015).

Patients with chronic obstructive pulmonary disease (COPD) may also develop OSA and the chronic bronchitis phenotype appears to be most susceptible (McNicholas, 2017). This phenotype is more prone to right heart failure, and the associated peripheral oedema may be an important factor in predisposing to OSA.

3.2.4 Nasal Obstruction

The primary route of breathing, especially while asleep, is through the nose, and there has been considerable interest in the role of nasal obstruction in the pathophysiology of OSA. The upper airway can be viewed as a Starling Resistor (Fig. 3.2) with the nose as the fixed inlet for breathing and the oropharyngeal airway as the collapsible segment leading to the fixed downstream segment of the lower respiratory tract (McNicholas, 2008b). This model supports a role for nasal obstruction in increasing upper airway collapsibility. Nasal obstruction can be fixed, such as occurs with a deviated nasal septum, or variable, as may be seen in seasonal rhinitis. The available evidence supports a role for variable nasal obstruction in the pathophysiology of OSA (McNicholas, 2008b; McNicholas et al., 1982), and active therapy of rhinitis with intranasal corticosteroids has been reported to reduce AHI in patients with mild to moderate OSA (Kiely et al., 2004). On the other hand, a randomized control trial of surgery for fixed nasal obstruction in patients with OSA reported little benefit in terms of AHI reduction (Koutsourelakis et al., 2008), supporting the view, somewhat surprisingly, that fixed nasal obstruction is not a significant factor in the pathophysiology of OSA.

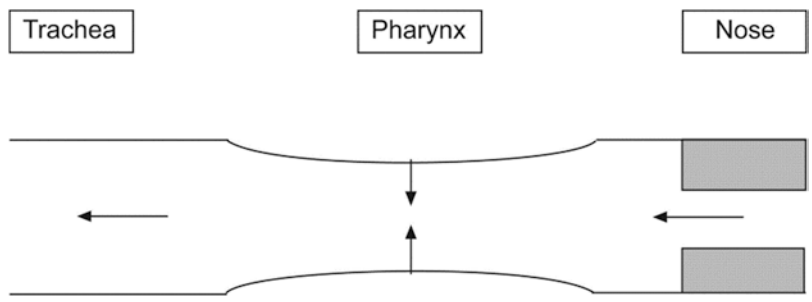

Fig. 3.2 Starling resistor model of the upper airway

3.2.5 Other Factors Influencing Upper Airway Calibre

The position of the head and neck has a significant influence on pharyngeal patency and varying head position between flexion and extension can cause significant variations in size of the retroglossal space and hyoid position on lateral cephalometry (Davies & Stradling, 1990). Neck flexion makes the upper airway more collapsible, whereas neck extension makes it more resistant to collapse, irrespective of changes in general body posture (Wilson et al., 1980). The supine posture also has an adverse effect on upper airway patency. Pharyngeal cross-sectional area is reduced from the upright to the supine position in both apnoeic and nonapnoeic snorers (Yildirim et al., 1991), and the supine posture effect appears to be due to gravitational forces acting to narrow the upper airway (Fouke & Strohl, 1987).

3.3 Upper Airway Dilator Muscle Function

The oropharyngeal airway is not a rigid structure and patency of this segment of the upper airway is dependent on the contraction of pharyngeal dilator muscles, especially the genioglossus, which act to stiffen the collapsible segment during inspiration (Deegan & Mcnicholas, 1995). These muscles contract in a phasic manner that is coordinated with inspiration and contraction of these muscles precedes the contraction of the diaphragm by milliseconds. Activity of these upper airway muscles is modulated by chemical stimuli, vagal input, changes in upper airway pressure, and baroreceptor activity (Brouillette & Thach, 1980).

In the setting of OSA, breathing through a narrowed upper airway generates a greater suction pressure and, thus, greater collapsing force, and pharyngeal dilator muscles must, therefore, contract more forcefully to prevent upper airway obstruction. This situation results in higher dilating muscle activity being evident during wakefulness, which diminishes to a greater extent than normal subjects during sleep, thus predisposing to upper airway obstruction (Mezzanotte et al., 1996). Progressive hypercapnia, hypoxia, asphyxia and negative pressure application all produce an augmenting drive to upper airway dilator muscles (Brouillette & Thach, 1980). Furthermore, genioglossus muscle activity varies with sleep stage, and is lowest in rapid-eye-movement (REM) sleep (Carberry et al., 2016), thus making the upper airway most collapsible in this sleep stage. This reduction across sleep stages is similar in patients with OSA to that seen in normal subjects and is similar in males and females (Eckert et al., 2009). Increased genioglossus muscle tone is associated with spontaneous periods of stable flow limited breathing in OSA and reductions in genioglossus activity during REM may explain the higher severity of OSA in that stage (Jordan et al., 2009).

The complexity of the upper airway musculature makes it unlikely that dysfunction of a single muscle group is responsible for OSA, but the genioglossus appears to be the most important, which pulls the tongue forward and opposes pharyngeal collapse. Muscles causing forward movement of the hyoid bone (geniohyoid, sternohyoid, and thyrohyoid) result in enlargement and stabilization of the pharyngeal airway, and the supine posture is associated with forward movement of the hyoid bone, which acts to limit the collapsibility of the airway in this position (Yildirim et al., 1991).

The degree of upper airway muscle preactivation prior to diaphragmatic contraction varies with respiratory drive (Strohl et al., 1980), and this could represent a compensatory attempt to open the airway before airway pressure is lowered by contraction of the diaphragm. Overall, the role of upper airway muscles in the pathophysiology of OSA appears to be more relating to inadequate compensation in the face of increasingly negative pressure during inspiration in patients with OSA, rather than a primary deficiency in the function of these muscles. This inadequacy is compounded by the observation that upper airway dilating muscles, as skeletal muscles, demonstrate a greater decrease in activity during sleep than the diaphragm as a normal

physiological response to sleep, especially during REM (Mezzanotte et al., 1996).

3.4 Respiratory Control

Contraction of the upper airway muscles and diaphragm respond in a similar manner to hypercapnia, hypoxia and airway occlusion (Brouillette & Thach, 1980), which suggests that central control mechanisms of upper airway and respiratory pump muscles in humans are closely related. However, there appear to be quantitative differences in the response to different stimuli. For example, oxygen breathing decreases genioglossal more than diaphragmatic electromyographic (EMG) activity, whereas hypercapnia and prolonged occlusion produce greater increase in genioglossal compared to diaphragmatic EMG (Brouillette & Thach, 1980).

The pattern of recurring apnoea frequently observed in OSA supports an instability of ventilatory control similar to periodic breathing and upper airway obstruction is most likely when diaphragmatic and genioglossal inspiratory EMG activity are at the lowest point of the cycle (Deegan & Mcnicholas, 1995). EMG activity progressively increases through the later stages of apnoea until the upper airway reopens, at which time the increase in genioglossal EMG is typically greater than that of the diaphragm (Dempsey et al., 2010). The period immediately following resolution of the apnoea is usually characterized by hyperventilation for several breaths, following which both EMGs then decrease in activity, which predisposes to further obstruction.

3.4.1 Apnoea Threshold

Normal subjects demonstrate fluctuations in ventilation associated with the transition from wakefulness to non-REM sleep, which is due to a reduction in the carbon dioxide (CO2) drive to breathe and the exposing of a sensitive apnoeic threshold that is critically CO2 dependent (Phillipson, 1978). The pivotal role of hypocapnia in this apnoea threshold is demonstrated by the observation that adding even small amounts of CO2 to the inspired air of patients with Cheyne Stokes Breathing can be sufficient to resolve the associated central apnoeas (Dempsey et al., 2010).

In OSA, the apnoea threshold is further amplified by the ventilatory overshoot that occurs after the termination of obstructive apnoea resulting in CO_2 reduction and thus predisposing to further apnoea. Such predisposition is initially towards central apnoea but the associated reduction in upper airway muscle activity contributes to upper airway collapse and associated obstructive apnoea. The CO_2-responsive apnoea threshold is particularly evident in non-REM sleep and there appears to be no evident threshold during phasic REM sleep (Skatrud & Dempsey, 1983). Furthermore, the periodic breathing associated with heart failure is rarely present in REM sleep. Additional factors that may contribute to further apnea post hyperventilation include lung stretch receptor and baroreceptor stimulation (Deegan & Mcnicholas, 1995).

3.5 Sleep Effects

During wakefulness, patients with OSA typically breathe normally, which is a consequence of the waking stimulus to breathe and associated tonic stimulation of the upper airway dilating muscles. However, with sleep onset, upper airway muscle tone diminishes, resulting in a more collapsible upper airway. EMG activity of the diaphragm and upper airway dilating muscles in healthy humans show reductions in amplitude associated with the transition from wakefulness to non-REM sleep, typically accompanied by a mild hypoventilation and a significant increase in upper airway resistance (Dempsey et al., 2010). Sleep is associated with a bigger reduction in upper airway EMG activity compared to that of the respiratory pump muscles, and this effect is greatest in REM sleep. This differential effect further compromises upper airway patency during inspiration.

The relative timing of phasic inspiratory EMG activity of the upper airway to diaphragmatic and

ribcage muscle activity varies during sleep in OSA (Hudgel & Harasick, 1990). Around the onset of obstruction, upper airway muscle EMG activity may fall behind the ribcage EMG, which facilitates airway collapse, but the normal pattern is restored as the apnoea progresses, thus facilitating airway reopening (Hudgel & Harasick, 1990). A clinical model of a disturbed timing relationship between upper airway and diaphragmatic contraction predisposing to OSA is seen in patients with diaphragmatic palsy treated with an electrophrenic pacemaker. Such patients are susceptible to OSA because the pacemaker results in diaphragmatic contraction at times other than when upper airway muscles contract.

3.5.1 Loop Gain

The predisposition to apnoea associated with recurring cycles of hyper/hypoventilation during sleep varies considerably relating to the respiratory control system gain and sleep state stability. Ventilatory instability depends on the loop gain of the respiratory control system. In general terms, loop gain refers to the stability of a system controlled by a feedback loop. In the context of respiratory control, loop gain refers to the gain of the negative-feedback loop that regulates ventilation in response to a ventilatory disturbance. Variations in loop gain may constitute an important potential contributing factor to obstructive apnoea. A high loop gain occurs where the magnitude of the increase in ventilation following apnoea is high, thus increasing ventilatory system instability and increasing the likelihood of subsequent apnoea.

Two types of respiratory control system gain are evident, namely plant gain and controller gain, which are both determinants of loop gain and consequent ventilatory stability. Plant gain relates to the background drive to breathe. A higher ventilatory drive protects against apnoea by requiring a larger additional transient hyperventilation and hypocapnia to reach the apnoeic threshold (low plant gain). Conversely, a reduced ventilatory drive and associated hypoventilation increases susceptibility to apnoea, by requiring only small transient ventilatory overshoots to reach the apnoeic threshold (high plant gain). Controller gain relates to chemoreponsiveness, especially the hypercapnic ventilatory response, and quantitively describes the slope of the change in ventilation in response to CO_2. An increased slope results in an increased susceptibility to apnoea even in the setting of background hyperventilation and low plant gain. However, loop gain can be difficult to measure, and there are few clinical studies that have explored this variable in the setting of OSA. Thus, the importance of loop gain as an inherent contributor to OSA pathophysiology remains uncertain.

3.5.2 Arousal

Termination of apnoea is usually associated with brain arousal, and thus, the arousal response may be an important protective mechanism (Eckert & Malhotra, 2008). However, the physiological events associated with arousal may have deleterious consequences that contribute to the pathophysiology of OSA, both by contributing to daytime sleepiness because of sleep disturbance, but more importantly, by predisposing to further upper airway collapse, thus predisposing to repetitive apnoeas (McNicholas, 1998). Studies of transient upper airway occlusion in normal sleeping subjects demonstrate that, if the occlusion is associated with arousal, hyperventilation and associated hypocapnia occurs following apnoea termination, whereas if no arousal occurs, hyperventilation is limited, and CO_2 may rise. OSA patients appear to more reliant on arousal at the termination of apnoea than normal subjects (Jordan et al., 2007). The post-apnoeic hyperventilation and fall in PCO_2 associated with arousal may reduce respiratory drive, and the resulting reduced drive to the UA muscles may predispose to further obstructive apnoea, and a repetitive cycle of recurring apnoeas may ensue (McNicholas, 1998). It has been proposed that arousal is not necessary for the upper airways to reopen and that the consequences of arousal at apnea termination are largely deleterious by promoting ventilatory instability (Younes, 2004). However, a recent report

indicated that the intensity of respiratory cortical arousals is a distinct pathophysiologic feature and is associated with disease severity in patients with OSA (Bahr et al., 2021).

Factors relating to obstructive apnoea that contribute to the arousal response include inspiratory efforts against an occluded airway, hypoxia, and hypercapnia. In humans, hypercapnia is a more important stimulus to arousal than hypoxia. Increasing ventilatory effort is an important factor in the arousal response, possibly mediated by mechanoreceptor feedback from respiratory muscles and/or from pressure-sensitive mechanoreceptors in the upper airway. Overall, increasing ventilatory effort appears to be the most important stimulus to arousal, and the stimulus to arousal from hypoxia and hypercapnia may be mediated principally through stimulating an increased ventilatory effort (Deegan & Mcnicholas, 1995).

The arousal response varies in patients with OSA and can be quantified by the arousal threshold. Experimentally, this threshold is measured as the minimum oesophageal pressure generated on the breath preceding arousal during a respiratory load or occlusion, and can be quantified non-invasively by polysomnography (Sands et al., 2017). As a group, OSA patients tend to have a higher arousal threshold than normal subjects, although there is considerable inter-subject variability in both groups. A low arousal threshold is an important potential contributing factor to OSA pathophysiology and may represent a therapeutic target in selected patients (Eckert et al., 2011).

3.6 Pathophysiological Endotypes and Phenotypes

The relevance of physiological, non-anatomic factors in the pathophysiology of OSA has been generating major interest in recent years (Randerath et al., 2018). These factors can be related to the underlying aetiology, referred to as endotype, and/or clinical manifestation, referred to as phenotype (Edwards et al., 2019), and may be viewed as a continuum from the genotype to personalized treatment options based on the individual endotype. Inadequate responsiveness of the genioglossus muscle, the arousal threshold, the critical closing pressure of the upper airway, and the stability of the respiratory control system defined by factors such as loop gain, define distinct endotypes of OSA that may be amenable to specific treatment approaches (Randerath et al., 2018). In one report of subjects with and without OSA, similar proportions of subjects, roughly one third each, had the endotypic traits of a minimal genioglossus muscle responsiveness during sleep, a low arousal threshold, or a high loop gain, and 28% of subjects had more than one of these traits (Eckert et al., 2013).

Phenotypes of pharyngeal dysfunction in OSA, such as collapsibility and pharyngeal muscle compensation, are evident from spontaneous changes in ventilation and ventilatory drive during sleep, which may be noninvasively assessed by polysomnography (Sands et al., 2018). There appear to be gender differences in OSA endotypes, with one report indicating that women demonstrate lower loop gain, less airway collapsibility, and lower arousal threshold in NREM sleep (Won et al., 2019), and endotypes explained 30% of the relative sex differences in NREM.

3.7 Integrated Pathophysiology

While the fundamental deficit in the pathophysiology of OSA relates to the inability of the upper airway dilating muscles to maintain a patent airway, the foregoing discussion indicates that many factors contribute to this basic pathophysiology. These factors vary in importance in different patients and in different sleep stages. For example, ventilatory drive withdrawal has recently been reported to be a more important mechanism of OSA than reduced genioglossus muscle compensation in REM sleep (Messineo et al., 2022). Overall, an insufficiency in drive to the upper airway dilating muscles for whatever reason, be it due to sleep-related factors such as the arousal threshold, respiratory control factors such as loop gain, or inadequate dilating muscle compensation, these factors interact to varying and overlap-

ping degrees to result in the increased negative intrapharyngeal pressure that is a consequence of airway narrowing being sufficient to collapse the oropharyngeal airway (Fig. 3.1).

3.8 Implications for Treatment

While the basic deficit of increased upper airway collapsibility in OSA can be readily reversed by CPAP therapy, a detailed understanding of the pathophysiology opens the potential for other management options and has the subject of extensive research, especially in recent years (Schütz et al., 2021). Inadequate upper airway dilating muscle compensation may be improved by targeted pharmacotherapy. Desipramine, which is a tricyclic antidepressant (TCA) that inhibits the norepinephrine reuptake receptor in the central nervous system, reduces the sleep-related loss of genioglossus activity and improves pharyngeal collapsibility in healthy humans (Taranto-Montemurro, Edwards, et al., 2016), and has been reported to reduce the AHI in OSA patients who demonstrate minimal genioglossus muscle compensation (Taranto-Montemurro, Sands, et al., 2016). Another norepinephrine reuptake inhibitor (atomoxetine) combined with an antimuscarinic (oxybutynin) have also been reported to substantially reduce AHI in patients with OSA (Taranto-Montemurro et al., 2019).

Sleep-induced reduction in respiratory motor neurone output can be reversed by electrical stimulation of the hypogossal nerve and this therapeutic approach is gaining support as a potential alternative therapy to CPAP (Heiser et al., 2021; Strollo et al., 2014). Acetazolamide may benefit OSA in selected patients with a high loop gain and has the added potential benefit of reducing blood pressure (Edwards et al., 2012; Eskandari et al., 2018). Diuretic therapy may also benefit OSA, especially in patients with fluid overload, by reducing nocturnal rostral fluid shift (Revol et al., 2020). Zolpidem increases sleep efficiency and the respiratory arousal threshold without changing sleep apnoea severity and pharyngeal muscle activity (Messineo et al., 2020).

Soft tissue accumulation in and around the oropharynx that contributes to airway narrowing can be treated medically or surgically, as appropriate. Children with adenotonsillar hypertrophy and OSA benefit from surgical removal (Stradling et al., 1990) and adults with OSA and central obesity benefit from weight reduction, induced by bariatric surgery (Currie et al., 2021) or medically by intensive dietary measures and/or pharmacological therapy (Chirinos et al., 2014). Liraglutide, which is a long-acting glucagon-like peptide one receptor agonist, has been reported to induce weight loss and lead to a significant reduction in AHI in patients with OSA (Blackman et al., 2016).

The role of oxygen therapy in the management of OSA is uncertain, although a recent report suggests that oxygen supplementation may benefit OSA acutely, possibly by reducing the arousal response (Joosten et al., 2021).

3.9 Conclusion

The complex pathophysiology of OSA offers opportunities to develop targeted therapy based on an understanding of the multiple interacting factors that contribute to upper airway collapse in individual patients. These measures offer the opportunity for precision therapy as an alternative to the established uniform therapy of CPAP.

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