Supplementary Data

OSA overview

OSA pathogenesis

Although the upper airway (UA) consists of rigid, cartilaginous structures, its patency can be compromised along a soft segment extending from the hard palate to the larynx (the pharynx), which allows the UA to change shape for speech and swallowing during wakefulness. However, in the presence of anatomically compromised upper airways (UAs), as in patients with OSA, the loss of wakefulness inputs to the control of the UAs and chest wall muscle motor neurons during sleep, produce UAs obstruction. The underlying mechanisms driving these UAs obstructions are complex and multi factorial (Figure 1 of the online supplement).

Patients with OSA have narrower UAs with enlarged surrounding soft tissues compared to healthy controls; thus increasing the risk of collapse during sleep (Figure 2 of the online supplement). During wakefulness, the UA dilator muscles (genioglossus most studied) activity is increased in patients with OSA, compared to healthy controls, compensating for the anatomically diminished UA size; while during sleep the UA dilator muscles activity is greatly reduced leading to pharynx collapse and subsequently UA obstruction, particularly during rapid-eye-movement (REM) sleep. This reduction in UAs muscle tone during sleep is due to a combination of central lack of respiratory drive and local inhibitory reflexes that respond to changes in pressure in the UAs. The chemoreceptors are also less responsive to PaO2 and PaCO2 changes during sleep, resulting in a reduced input to the respiratory centers in the brainstem and reduced UA dilators activity. Even very small and transient reductions in PaCO2 can result in significant apnoea due to the changes in chemoreceptors activity during sleep. The reduced UA dilator muscles activity is also due to reduced mechanoreceptors’ responses to changes in negative UA pressure (genioglossus negative pressure reflex) during REM.

Respiratory arousal threshold (RAT) also plays an important role in the pathogenesis of OSA in some patients. In response to changes in gas exchange, pH, lung volumes or UAs resistance, the respiratory centres in the brainstem can increase respiratory effort, which triggers an arousal from sleep when RAT is reached. Hence, arousals are protective as they increase UA muscle tone (similar to the awake state) and finally open obstructed UAs. However, low RAT can have detrimental effects in patients with OSA as more frequent...
arousals can result in a disruption in sleep architecture and in restoring airflow before the development of adequate ventilatory drive and result in ventilatory overshoot associated with the sleep/wake transition leading to further obstructive episodes\textsuperscript{1, 2, 20-23}.

Another important element in OSA development is the ventilatory control stability, known as loop gain, which refers to the size of a “ventilatory correction” as a response to a “ventilatory disturbance”\textsuperscript{2, 24}. Accordingly, in case of a high loop gain, small decrease in breathing will lead to a large correction. In the case of OSA, the loop gain appears to be elevated\textsuperscript{25}, suggesting high responsiveness of the ventilatory system to disturbed breathing with a propensity to develop cyclical fluctuations in breathing output and increased response to arousal by hyperventilation driving PaCO\textsubscript{2} below the apnea threshold\textsuperscript{1, 26, 27}.

There are multiple other factors that contribute further to the pathogenesis of OSA and UA collapsibility including low lung volume (resulting in lack of pharyngeal stretching), reduced UAs surface tension and UA oedema\textsuperscript{2, 28-32}.

**OSA risk factors**

Excess body weight is the main risk factor for OSA\textsuperscript{33}. Weight gain of 10% is associated with a 6-fold higher risk of moderate to severe OSA development\textsuperscript{34}. Similarly, 9% weight loss in patients with obesity and OSA results in 47% reduction in apneas frequency\textsuperscript{35} and 60% reduction in the Apnoea- Hypopnoea index (AHI) after 17% drop in BMI\textsuperscript{36}. Men have consistently been shown to be at a 2- to 3-fold higher risk of OSA compared to women\textsuperscript{37}; possibly due to differences in sex hormones which will be detailed later. Multiple studies showed African-Americans to be at increased risk of OSA compared to White Caucasians\textsuperscript{38-40}. Whereas, differences in the prevalence of OSA in Asians vs. white Caucasians were inconsistent across multiple studies\textsuperscript{38, 41-42}. The ethnic variations could be related to differences in UA anatomy, respiratory arousal thresholds, fat distribution, genetic and environmental factors\textsuperscript{37, 41-45}. Prevalence of OSA increases with increasing age\textsuperscript{33}, being 2-3 fold higher in older people (≥65y), reaching eventually a plateau after the age of 65\textsuperscript{37}. Other risk factors include smoking, excess alcohol intake, nasal obstruction and menopause\textsuperscript{37}.

**OSA clinical features**

Snoring is the most frequent OSA symptom\textsuperscript{symptom} but it is not diagnostic for the disease, as most snorers don’t have OSA and\textsuperscript{46}; only 6% of patients with OSA do not report snoring\textsuperscript{46}, but it is very frequent in general population as well\textsuperscript{46}. Other clinical features include, witnessed apneas, nightly chocking and gasping (reflecting an arousal after an apnea event), insomnia, nocturia, enuresis, arousals, sweating\textsuperscript{47}, excessive daytime sleepiness (EDS), and a
variety of other daytime symptoms such as fatigue, memory loss, irritability, morning headaches, depression, and erectile dysfunction \(^{46, 48}\).

**OSA comorbidities and associations:**
OSA is associated with significant comorbidities such as hypertension, Type 2 diabetes, cardiovascular disease, mortality, road traffic accidents, chronic kidney disease amongst others \(^{4, 47, 49, 50}\).

**OSA diagnosis and treatment:**
Multiple definitions of OSA have been used in clinical research, which contributed to some of the variations in outcomes of studies in patients with OSA. OSA is generally diagnosed based on cut offs of parameters recorded during polysomnography or polygraphy. The AHI is defined as the average number of apnoea and hypopnea events per hour of sleep. The respiratory disturbance index (RDI) is defined as the AHI plus the respiratory-effort related arousals. The oxygen desaturation index (ODI) is the average number of oxygen desaturation per hour of sleep. The American Academy of Sleep Medicine (AASM) recommendations regarding OSA diagnosis and the criteria used to define apnoea and hypopneas are detailed here \(^{51, 52}\).

Polysomnography remains the gold-standard for diagnosing OSA, although multiple portable devices have also been considered appropriate if adequate channels are recorded according to the latest AASM guidelines \(^{52}\). Sleep staging is desirable but not always considered essential. CPAP is the gold standard treatment for patients with moderate to severe OSA in addition to weight loss in patients with obesity \(^{48, 53, 54}\). Intra oral devices can be used in mild OSA and more recently upper airway stimulation can also be used in certain patients groups \(^{55, 56}\).

**Literature**


