Published in final edited form as:
Indian J Med Res. 2010 February ; 131: 176–187.

Pathophysiology & genetics of obstructive sleep apnoea

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Abstract

Obstructive sleep apnoea (OSA) is a highly prevalent condition with proven neurocognitive and cardiovascular consequences. OSA patients experience repetitive narrowing or collapse of the pharyngeal airway during sleep. Multiple factors likely underlie the pathophysiology of this condition with considerable inter-individual variation. Important risk factors for OSA include obesity, male gender, and ageing. However, the mechanisms underlying these major risk factors are not well understood. We briefly review the state-of-the-art knowledge regarding OSA pathogenesis in adults and highlight the potential role of genetics in influencing key OSA pathophysiological traits.

Keywords

Arousal; genioglossus; lung; obstructive sleep apnoea; upper airway; ventilatory control stability

The obesity pandemic is affecting global health in a variety of ways. One of the major respiratory manifestations of obesity is in the form of obstructive sleep apnoea (OSA). Sleep apnoea is defined by recurrent reductions (hypopnoeas) or stoppages (apnoeas) in breathing during sleep as result of pharyngeal airway narrowing or collapse[1]. OSA is defined by reduction in airfow in the presence of ongoing respiratory efforts[2–4]. In contrast, central sleep apnoea is characterized by the absence of respiratory effort during airfow attenuation[5]. Obstructive apnoea is considerably more common than central apnoea and is the focus of the present manuscript. In OSA, hypoxemia and hypercapnia result from these breathing disruptions with the ultimate result being catecholamine surges and associated hemodynamic consequences[6,7]. Loud snoring, caused by vibration of pharyngeal tissues, is a classic symptom of OSA[8]. In most but not all cases the termination of respiratory events is associated with electrocortical arousal from sleep[9,10]. These repetitive events result in a cyclical breathing pattern and sleep fragmentation as the patient fluctuates between wake and sleep[11,12]. Severe sleep apnoea patients can experience respiratory events in excess of 100 times per hour with each event, by definition, lasting at least 10 sec.

Symptomatic OSA affects at least 2–4 per cent of the US population[13]. Prevalence estimates from around the world support similar values[14], and numbers are likely to increase with the obesity pandemic[15]. Sensitive indices of airflow (nasal pressure)[16] and the realization that asymptomatic patients may have complications of OSA[17] have both contributed to higher estimated prevalence. While non obese individuals may suffer from OSA, obesity is the

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main epidemiological risk factor. Indeed, increases in body mass index, central accumulation of adipose tissue, and neck circumference are strong predictors of this disease[18]. Although obesity is a major risk factor for OSA, roughly 30 per cent of patients with obstructive sleep apnoea syndrome are not obese, emphasizing the need for a high index of suspicion in clinical practice. Further, the prevalence of OSA is 2–3 times greater in men than in women and in older compared to middle aged individuals[19]. Menopause is a well established risk factor for OSA in women[20].

OSA can yield major neurocognitive manifestations including excessive daytime sleepiness/fatigue, impaired cognition, reduced quality of life, and an up to seven fold increased risk of road traffic accidents[21–24]. Treatment of OSA leads to improvements in many of these outcome measures[23,25]. There is evolving evidence to support the role of OSA as an independent risk factor for adverse cardiovascular sequelae. Although some argue that OSA was simply a marker of an unfit patient group[26], rigorous recent studies have shown that OSA is causally linked to a number of important sequelae. OSA is now a well established risk factor for hypertension (both incident and prevalent), stroke and probably myocardial infarction, congestive heart failure and death[27–31]. OSA has been causally linked to the development of hypertension based on large rigorous cross-sectional and longitudinal epidemiological studies, mechanistic animal studies and most recently interventional trials[32–37].

The underlying causes of OSA vary considerably between afflicted individuals. Important components likely include pharyngeal anatomy[38,39], pharyngeal dilator muscle responsiveness to respiratory challenges during sleep[40–43], the arousal threshold (propensity to wake up from sleep)[44,45], the instability of the negative feedback control system regulating ventilation (loop gain)[46–48], and upper airway tethering via caudal traction from changes in end-expiratory lung volume (EELV)[49–52]. These various physiological traits and the potential for each to influence OSA have been described in detail elsewhere[53]. The focus of the current article will be to review the key pathophysiological factors and their interactions, to highlight recent innovations in our understanding of OSA pathogenesis, and to summarize the existing literature regarding the genetics of sleep apnoea[3].

Pathophysiology

Anatomical and biomechanical factors

The evolution of speech in man, which demanded considerable laryngeal motility, yielded the human upper airway vulnerable to collapse based on its reliance on muscles and soft tissues to maintain pharyngeal patency. The anatomy and neural control of the upper airway has evolved to facilitate multiple functions including speech, swallowing and ventilation. Most notably, the upper airway is vulnerable to collapse throughout its length from the hard palate to the larynx[54].

People with sleep apnoea have a smaller pharyngeal airway than do matched controls[55–57]. Multiple imaging and physiological studies have shown compromise of the pharyngeal luminal cross-sectional area in OSA as compared with controls[39,57,58]. Further, the soft tissue and bony structure surrounding the lumen appears to be altered in OSA patients which may place it at risk for collapse. Imaging studies during wakefulness, however, are complicated to interpret since ongoing pharyngeal dilator muscle activity (greater in OSA than controls[59]) may lead to observed differences between groups based on non anatomical (*i.e.*, neuromuscular) factors. The critical closing pressure (Pcrit) is commonly used to quantify pharyngeal collapsibility[60], with very negative values suggesting a stable upper airway and very positive values suggesting an unstable pharynx. The Pcrit can be measured both passively (as an index of anatomy) or actively (indicative of both anatomical and

neuromuscular control)[61,62]. Passive Pcrit studies support increased propensity of the OSA airway to collapse on a purely biomechanical basis[63]. Perhaps the most persuasive data come from a study by Isono *et al*[63] who observed increased closing pressure (more collapsible) in OSA as compared to controls under conditions of general anesthesia and muscle paralysis. Thus, in aggregate, multiple methodologies have shown that OSA patients have anatomical compromise leaving these individuals vulnerable to pharyngeal collapse during periods of susceptibility such as sleep and anaesthesia[64].

Upper airway dilator muscle activity and recruitability

Patients with OSA have increased pharyngeal dilator muscle activity (as a percentage of maximum) versus matched controls[59] that has been interpreted as evidence for neuromuscular protective compensatory reflexes in response to anatomical compromise in OSA. Through these protective reflexes, the increased muscle activity protects pharyngeal patency during wakefulness[42,65]. Although some data have suggested that increased pharyngeal dilator muscle activity is a result of denervation, these data are controversial. For example, if denervation was the critical factor underlying increased muscle activity, the mechanisms important in maintaining pharyngeal patency during wakefulness in OSA would remain unknown. One important pathophysiological mechanism relates to the ability of the upper airway dilator muscles to maintain a patent airway during sleep. In support of this concept, standard multi-unit genioglossal electromyogram activity is reduced at sleep onset in healthy individuals and OSA patients[66]. Thus, while healthy individuals experience a loss of upper airway muscle tone at sleep onset (alpha-theta transition in the electroencephalogram) and experience some degree of breathing instability, an individual reliant on muscle tone due to an anatomical vulnerability will be particularly susceptible to apnoea. As one might predict, hypopnoeas and apnoeas frequently occur at the transition from wakefulness to sleep in OSA[12,67]. Each respiratory event is typically associated with an electro-encephalographic arousal such that the OSA patient cycles between wakefulness and sleep leading to minimal deep sleep. Unlike the transition to sleep, slow wave sleep is associated with increased, not decreased, upper airway dilator muscle activity in the majority of studies[68,69]. Some have argued that deep sleep is a state of intrinsic stability with associated increases in upper airway dilator muscle activity being one important factor contributing to the improvement in apnoea severity[68,69]. The high arousal threshold (low propensity to wake up) and neurochemical milieu seen in slow wave sleep may also be important factors stabilizing breathing. On the other hand, slow wave sleep could simply be a marker of breathing stability such that delta sleep (N_3) may only occur when respiratory arousals are not occurring[68,69]. This controversy is difficult to resolve since the direction of causation is unclear. That is, whether deep sleep stabilizes breathing or breathing stability permits deep sleep to occur is uncertain. However, pharmacological studies using agents to promote slow wave sleep may be one method to test this hypothesis.

Multiple factors can influence output from the hypoglossal motor nucleus to the major upper airway dilator muscle (the genioglossus)[70–76]. Respiratory drive from the central pattern generator in the brainstem is a major determinant of genioglossus activity[77,78]. In addition, local upper airway mechanoreceptors respond to subatmospheric (negative or suction) pressure and modulate genioglossus activity[79–82]. The negative pressure reflex describes the phenomenon whereby the genioglossus (and other upper airway dilator muscles such as the tensor palatini) is activated in response to negative pressure (*i.e.*, suction pressures which promote pharyngeal collapse)[83,84]. Thus, pharyngeal patency can be protected by a robust activation of the dilator muscles in the face of a collapsing perturbation. This negative pressure reflex has been shown to be attenuated during stable non rapid eye movement (NREM) sleep in healthy individuals[83,84]. That is, the ability of the upper airway to maintain patency in the face of a collapsing stimulus is impaired during sleep. However, recent data

have shown a maintained reflex during NREM sleep, particularly in the supine posture when the upper airway is most vulnerable to collapse[40,85–88]. Indeed, our understanding of the neuroanatomy of the genioglossus negative pressure reflex and hypoglossal motor nucleus inputs from rat studies has recently evolved[89]. Although pharyngeal dilator muscle responsiveness is likely impaired during NREM and REM sleep[90], the genioglossus can respond to both sustained mechanoreceptive (negative pressure) and chemoreceptive stimuli, particularly when combined stimuli are present[91]. The implication of this finding is that, given sufficient time and magnitude of stimuli, the upper airway dilator muscles will eventually respond to respiratory stimuli, *e.g.*, CO_2 plus negative pressure[92–95]. Thus, in the setting of pharyngeal collapse, airway patency may be restored if upper airway muscles respond sufficiently before arousal occurs. Because intrathoracic pressure appears to be both the stimulus for arousal from sleep and closely related to the stimulus for genioglossal activation[96–98], ventilatory drive can yield two competing mechanisms (*i.e.*, arousal vs. restoration of airway patency)[9,99]. Not surprisingly, there is considerable inter-individual variability in the effectiveness of these compensatory mechanisms to restore airflow during sleep[92], which may in part be due to high variablily in the respiratory arousal threshold.

Although traditional electromyogram (EMG) studies have been informative, such studies have relied on multiunit recordings which obscure the activity of individual motor units contributing to overall activity. High frequency sampling techniques have recently been used to define single motor units (SMUs) within the genioglossus with illuminating results[100–103]. These SMU techniques allow sorting of individual motor units within the muscle of interest to gain insight into muscle characteristics and regulation using electrophysiology. These SMU techniques have been used extensively in muscle physiology, but have only recently been rigorously applied to human upper airway muscles with a view towards understanding sleep apnoea pathogenesis. These SMU techniques when applied to the genioglossus electromyogram allow insights into cellular activity within the hypoglossal motor nucleus. Although research is ongoing, studies have already shown considerable complexity within the genioglossus muscle[100]. By combining neuroanatomical and neurochemical experiments in rodents with sensitive neurophysiological techniques in humans, major insights into motor control are likely to occur yielding the possibility of novel therapeutic targets for some OSA patients[3]. While, such targeted approaches may lead to improvements in OSA, given the heterogeneity of OSA pathogenesis, such an approach is unlikely to resolve respiratory events for all patients.

Arousal from sleep

Arousal from sleep at the termination of a respiratory event is an important protective mechanism to restore pharyngeal patency[9]. In fact, most, but not all, respiratory events are associated with cortical arousal[104]. However, Younes[9] has emphasized the notion that arousal is not essential for restoration of airflow. By applying intermittent continuous positive airway pressure (CPAP) reductions in OSA patients, Younes observed that inspiratory flow increased in 22 per cent of instances prior to arousal and was restored in 17 per cent of trials in the absence of EEG arousal. Subsequently, findings of a study by Jordan and colleagues[92] suggest that these restorations in airflow without arousal may be mediated by genioglossus activation. In this study, challenges to pharyngeal patency (through CPAP drops) for up to 5 min resulted in genioglossus activation and changes in respiratory duty cycle (*i.e.*, inspiratory time prolonged relative to expiratory time). These compensatory responses were similar between OSA patients and healthy individuals, although OSA patients were less able to restore ventilation without cortical arousal than controls. During a subsequent study (unpublished observations), physiological variables were recorded during periods of spontaneously occurring stable and unstable breathing. Jordan *et al*[92] observed that genioglossus activity was likely responsible for these stable breathing periods. That is,

during periods of stable breathing, genioglossal activity was high relative to unstable periods, whereas tensor palatini activity and end-expiratory lung volume were essentially unchanged. However, the therapeutic implications of this observation are unclear. Questions remain as to how these stable breathing periods can be induced *e.g*., by giving a hypnotic agent to raise the arousal threshold in patients with recruitable upper airway muscles[105,106]. For example, a hypnotic agent provided to OSA patients with a low arousal threshold but recruitable upper airway muscles may allow enough time for CO_2 and negative pressure to accumulate sufficiently to augment dilator muscle activity yielding improvements in pharyngeal patency. On the other hand, a hypnotic agent may be deleterious if prolonged apnoeas occur with marked hypoxemia and insufficient muscle recruitment to restore pharyngeal patency (Figs 1 and 2). Further work is clearly needed in this area to define the subgroup of OSA patients who may or may not respond to manipulations in the arousal threshold.

Most of the available evidence suggests that the level of intrapleural pressure, generated by respiratory effort is a major stimulus triggering arousal from sleep (Fig. 3)[44,96]. Experimentally, the respiratory arousal threshold is measured as the nadir oesophageal pressure (or minimum epiglottic pressure which is similar to oesophageal during airway occlusion) generated on the breath preceding arousal from a respiratory event or perturbation[106]. Although the arousal threshold values are highly variable between individuals, patients with OSA tend to have an impaired arousal response to airway occlusion (more negative pressure required for respiratory arousal) than controls[99]. However, the question remains as to whether the higher arousal threshold observed in OSA is a cause or a consequence of the disease. Studies examining the impact on arousal threshold in OSA with nasal CPAP therapy suggest some improvement (lowering) of arousal threshold as compared with untreated OSA[44,107,108]. These data suggest that an elevated arousal threshold in OSA may be at least in part acquired from the disease.

Following arousal from sleep, augmented pharyngeal dilator muscle activity and a robust ventilatory response to arousal generally occur (Fig. 3)[109]. While these events are beneficial in restoring airflow and improving gas exchange, these changes can also be destabilizing and may perpetuate apnoea. That is, the ventilatory response to arousal can drive down carbon dioxide levels below the apnoea threshold such that apnoea can occur during subsequent sleep[5,110–112].

Loop gain (ventilatory control stability/instability)

Another characteristic feature of OSA is the cyclical breathing pattern that develops whereby the patient oscillates between obstructive breathing events (sleep) and arousal (wakefulness). Further, obstructive events tend to occur during periods of low respiratory drive. Thus, instability in ventilatory control is likely a critical contributor to OSA.

Loop gain is an engineering term that is used to describe stability or instability in a negative feedback control system[113–115]. The regulation of room temperature provides a useful analogy whereby temperature will be prone to oscillation when there is a sensitive thermostat and an overly powerful heater (*i.e*., high loop gain). The room temperature analogy can be used to understand the impact of sensors and effectors on temperature stability[12]. In the context of ventilatory control, loop gain refers to the stability of the ventilatory control system and how responsive the system is to a perturbation to breathing[47,95,116–120]. That is, loop gain is the propensity for the ventilatory control system to develop fluctuations in ventilatory output (as seen in periodic breathing). There are three major components to loop gain: controller gain, plant gain and mixing gain[12]. In control of breathing, controller gain refers to the chemoresponsiveness of the system [*i.e*., chemosensitivity (hypoxic and hypercapnic ventilatory responses) plus responsiveness][121].

Plant gain primarily reflects the efficiency of CO_2 excretion (*i.e*., the ability of a given level of ventilation to excrete CO_2). Mixing gain appears to be less crucial, but is a function of circulatory delay as well as hemoglobin binding of O_2 and CO_2. Mixing gain tends to be fairly constant, although circulatory delays may make mixing gain more clinically relevant in patients with congestive heart failure[122,123]. A high loop gain system is present if periodic breathing develops in the setting of minimal perturbation whereas a low loop gain system remains stable despite major perturbation. Younes has developed techniques to measure loop gain, including one using proportional assist ventilation (PAV)[116,124,125]. PAV studies have shown that OSA patients have an elevated loop gain compared to controls and suggest that ventilatory instability is an important mechanism underlying OSA. However, the PAV technique uses expiratory positive airway pressure (EPAP) which stabilizes the upper airway and relies on stable sleep without arousals[119]. Thus, transient events which may be important in perpetuating cyclical breathing may be neglected by this technique.

Why high loop gain leads to sleep apnoea is unclear. There are two major possibilities. First, elevated loop gain may increase oscillations from the brain stem pattern generator. In theory, pharyngeal patency should be maintained during high output to the phrenic and hypoglossal nerves[117]. On the other hand, pharyngeal obstruction may occur when central motor output to the upper airway is at its nadir. Second, elevated loop gain may also augment the ventilatory response to arousal[126,127], which would drive $PaCO_2$ (partial pressure of CO_2 in arterial blood) below the apnoea threshold. Obstructive or central apnoea would then occur depending on the prevailing upper airway mechanics. Thus, further work is clearly required in this area.

Functional residual capacity (End-expiratory lung volume)

Lung volume effects on pharyngeal patency are likely to be important in OSA pathogenesis. Clearly, upper airway mechanics can be affected by alterations in end-expiratory lung volume during wakefulness and sleep in healthy individuals. Hoffstein and colleagues[128,129] demonstrated that pharyngeal cross-sectional area changes from residual volume (RV) to total lung capacity (TLC). This lung volume dependence on the upper airway appears to be more pronounced in OSA patients versus controls. However, studies during wakefulness are confounded by behavioural influences since a maximal inhalation to TLC is likely to activate upper airway muscles volitionally. During sleep, upper airway resistance increases as lung volume falls. Increasing end expiratory lung volume decreases airway collapsibility in healthy controls and improves respiratory mechanics in OSA patients[49,52,130–132].

While studies have demonstrated that changes in lung volume may modulate upper airway patency in OSA, the underlying mechanisms are poorly defined[130–132]. A loss of caudal traction on upper airway structures may occur with reduced lung volume. When lung volume falls, the diaphragm migrates upward (cephalad), potentially resulting in a loss of caudal traction forces on the upper airway, and yielding a more collapsible upper airway. Conversely, elevated end-expiratory lung volume may lead to increased caudal traction and a more stable upper airway. Whether lung volume per se can be targeted therapeutically remains unclear, although part of the benefit of CPAP may be from augmentation of end-expiratory lung volume.

Influence of genetics on key OSA pathophysiological traits

A familial predisposition for OSA has been recognized for nearly 40 years since Strohl *et al*[133] described a family with multiple affected relatives. Since that time, multiple studies have demonstrated that individuals who have a family member with OSA are at increased risk of having apnoea themselves[134,135]. Redline *et al*[136] reported a dose-response curve such that compared to an individual with no affected relatives, having 1, 2, or 3 or more

relatives with OSA increases one's own risk by 1.5,2, and 3-fold respectively. Studies in both Caucasians and African-Americans as well as in the elderly have consistently found that approximately 1/3 of the total variance in apnoea / hypoapnoea index (AHI) can be explained by familial factors[137–139].

Since obesity has a strong genetic basis with 60–80 per cent of the variance in BMI explained by familial factors[140,141], some have postulated that perhaps the genetic basis for OSA is simply secondary to genes influencing levels of adiposity. Several lines of work suggest that this is not the case. Mathur & Douglas[135] found that relatives of lean OSA patients were at increased risk of sleep apnoea themselves. Bivariate modeling in the Cleveland Family Study has found that approximately 40 per cent of the genetic basis defining AHI is explained by obesity leaving the majority of genetic variance in AHI mediated through obesityindependent mechanisms[142].

Upper airway anatomy represents one potential obesity-independent genetic pathway. Bony facial features relevant to OSA such as length of the cranial base and the nasion-sella-basion angle demonstrate substantial heritability[143]. Relatives of people with OSA are more likely to have retro-positioned maxillae and mandibles[135]. In addition, the cephalic index (ratio of head width to head length) is almost completely genetically determined[144]. MRI studies demonstrate that soft tissue structures such as tongue and lateral pharyngeal wall volume also have a genetic basis with over a third of the variability in these structures explained by familial factors[145].

Ventilatory drive may represent another mechanism by which genes influence OSA susceptibility. Ventilatory responses to hypoxia and to inspiratory resistive loading have been found to have a familial basis and be impaired in relatives of OSA patients compared to relatives of controls[146–148]. Also supporting a role for ventilatory control genes in defining OSA risk has been the finding that cases of OSA and sudden infant death syndrome (SIDS) co-segregate within families[149–151]. Other potentially important pathways in OSA pathogenesis such as airway dilator muscle tone and responsiveness, upper airway neural reflexes, and arousal threshold may also have genetic underpinnings; however, no studies have yet been performed to assess the familial basis for these traits directly. Thus, the definition of phenotypic traits may facilitate genetic investigations of complex diseases by allowing more precision *i.e*., there is unlikely to be a single gene for sleep apnoea but there may well be a predominant gene defining variability in arousal threshold, for example.

In terms of identifying causal genes, several whole genome linkage analyses have been performed with identification of possible candidate regions but in general these results have not been consistent[137,138,152]. Many candidate gene association studies have been performed with a growing number of positive results reported[153–156]. However, similar to work on the genetics of other complex diseases, for the most part these studies have been underpowered and difficult to replicate suggesting a high likelihood of the positive results representing false positive findings. The most consistently demonstrated association has been between OSA and the ε4 allele of the apolipoprotein E (APOE) gene. This allele, known to predispose to Alzheimer's dementia, has been found to predict a greater AHI in the Wisconsin Sleep Study and Framingham Study[157,158]. However, these findings have not been replicated in other large cohorts[159,160]. The success of large scale genome wide association studies recruiting tens of thousands of patients to identify novel risk genes in diseases such as asthma, diabetes, and Crohn's disease has raised interest in using such a study design for OSA. Efforts are underway to begin such large scale collaborative studies in the sleep-disordered breathing field.

Acknowledgments

Dr Malhotra has received consulting and/or research funding from Respironics, NMT Medical, Itamar Medical, Cephalon, Pfizer, Apnex Medical, Restore Medical, Inspiration Medical, Medtronics, and Sepracor. Ms. Campana, Drs. Eckert and Patel report no conflicts. Dr Eckert is supported by an Overseas Based Biomedical Fellowship from the National Health and Medical Research Council of Australia (510392). Dr Patel is PI on NIH HL081385 and ATS Research Program Award. Dr Malhotra is PI on NIH P50 K24HL093218, RO1-HL73146, RO1-HL085188-01, RO1HL090897 and AHA Established Investigator Award.

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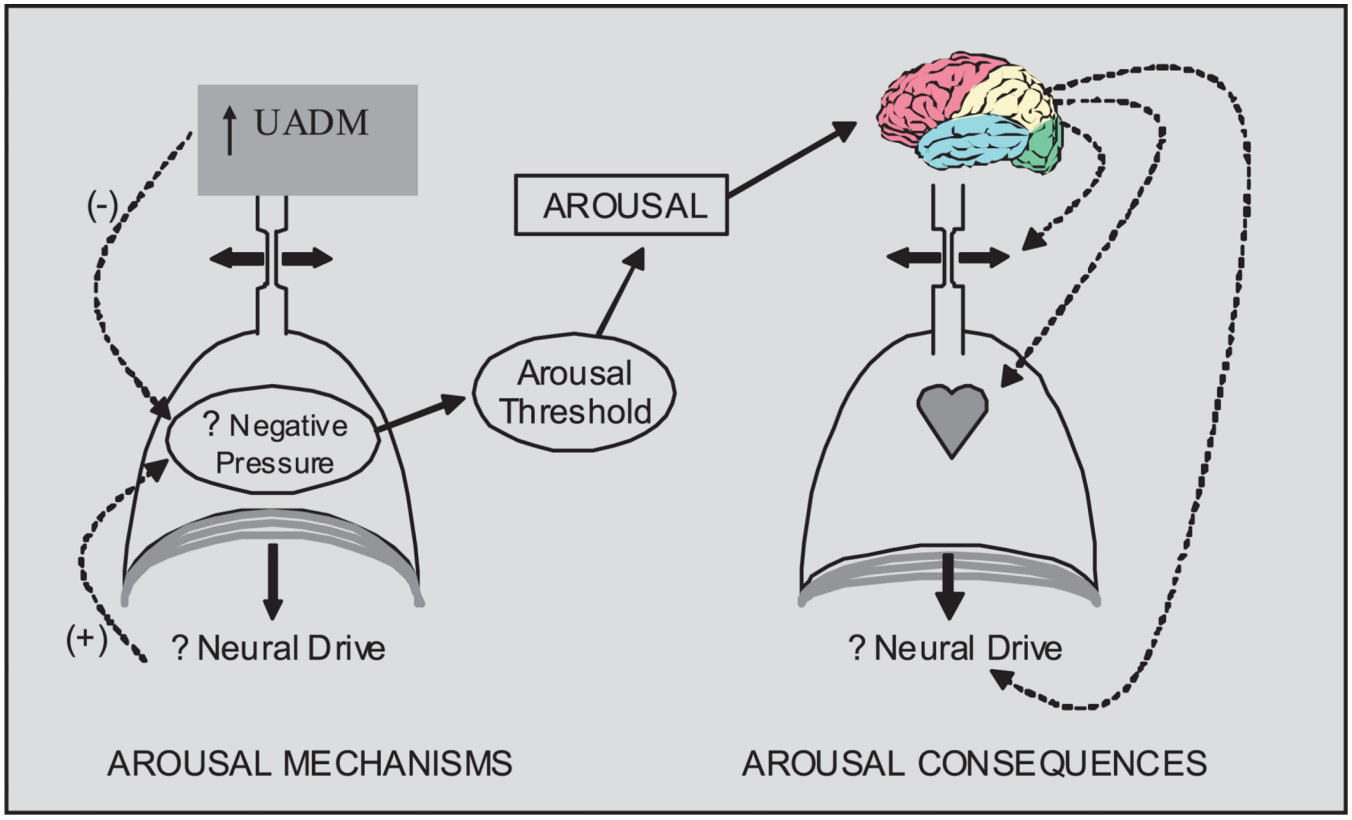

Fig. 1.

The role of UADM (upper airway dilator muscles) in stabilizing breathing. Negative intrathoracic pressure plus CO_2 can activate UADM, but negative pressure can also trigger arousal. A hypnotic could potentially change the arousal threshold to stabilize breathing and potentially prevent the consequences of repetitive arousal.

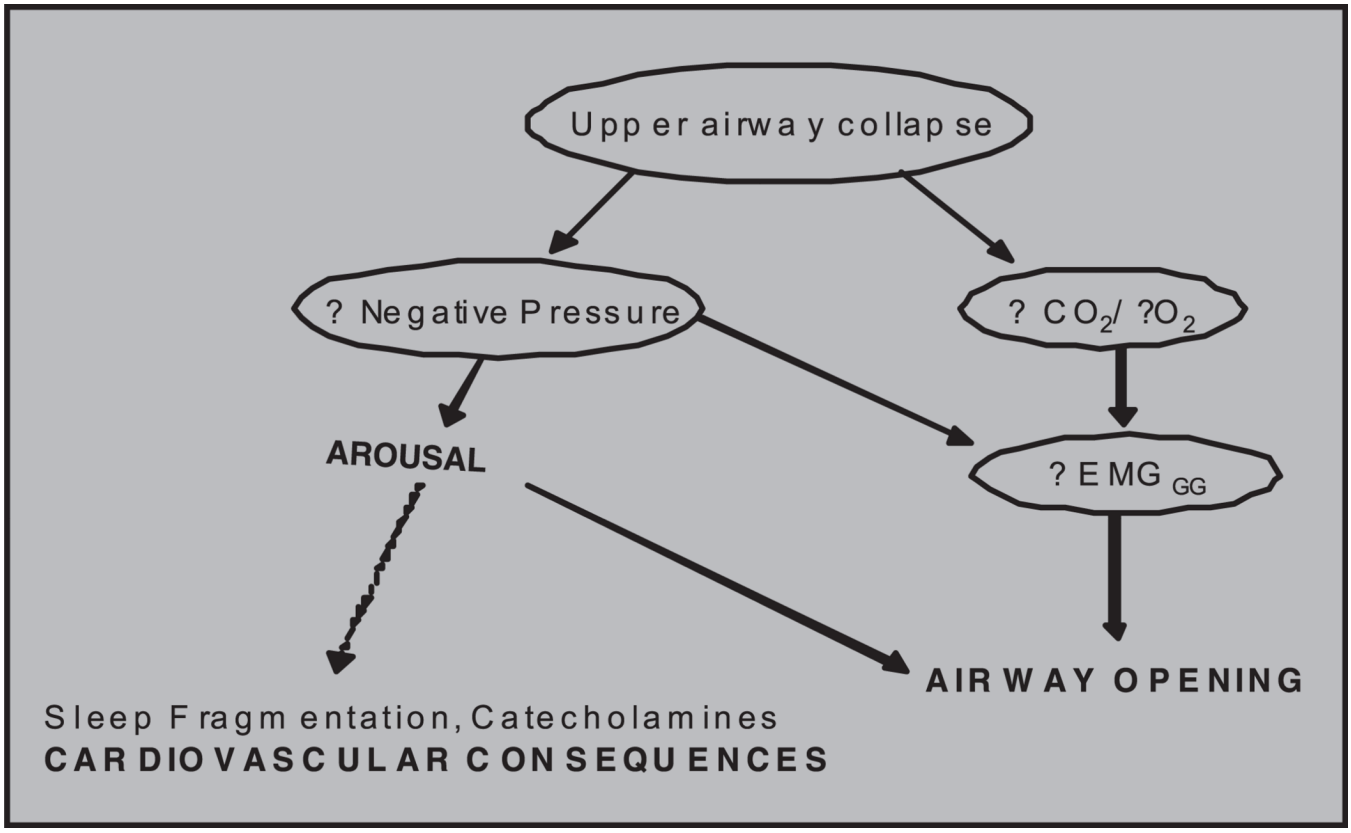

Fig. 2.
The double edged sword of arousal leading to both airway opening and possible cardiovascular consequences. Airway opening can be achieved without arousal by activating genioglossus (EMG_{GG}) through negative pressure plus CO_2.

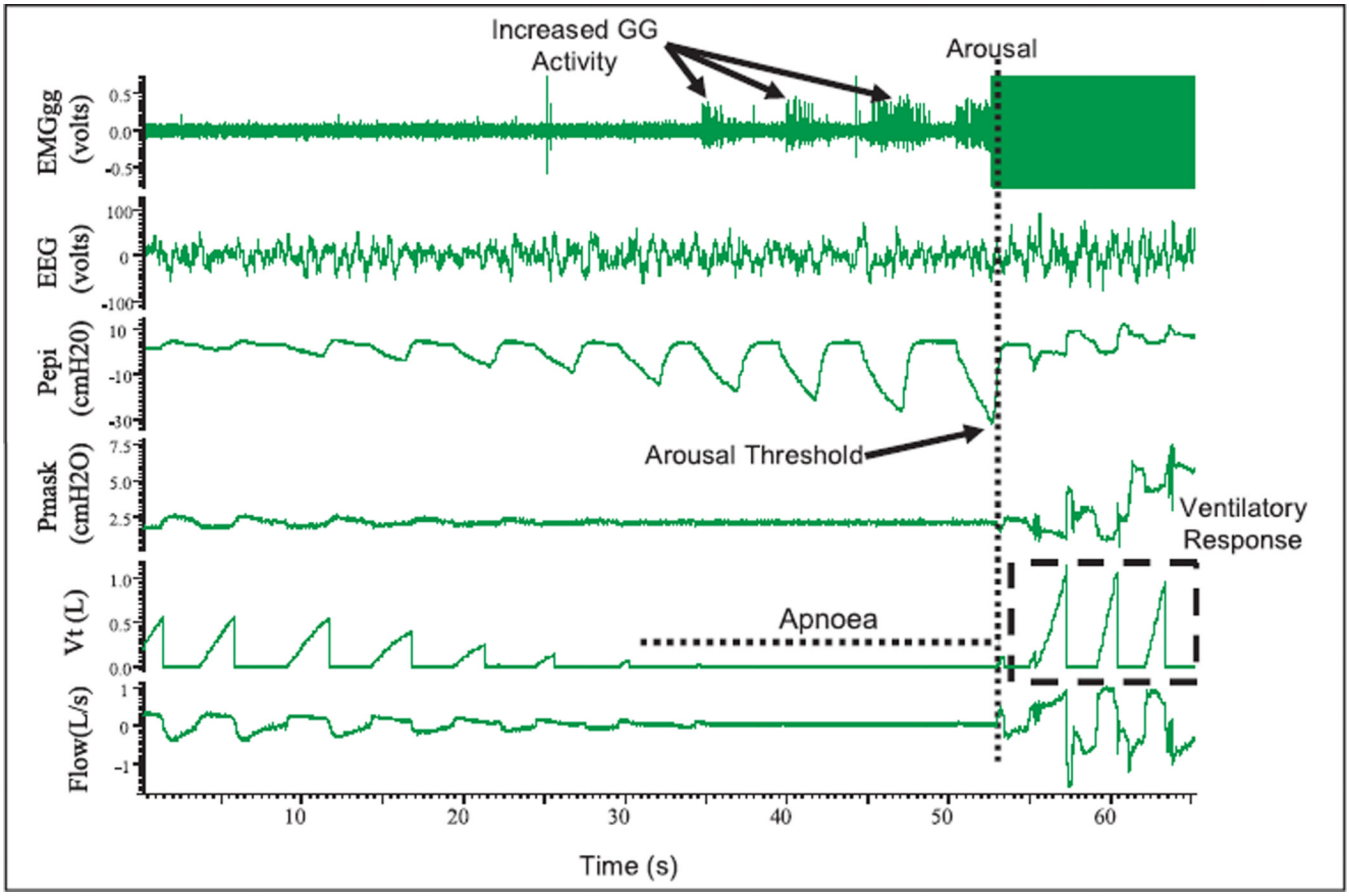

Fig. 3.

Example polysomnographic tracings of an obstructive sleep apnoea event induced by reducing continuous positive airway pressure (from therapeutic to 2cmH_2O) in a 52 yr old male patient with severe OSA (apnoea/hypopnea index= 34.5 events per hour). EMGgg= Electromyogram of the genioglossus muscle (intramuscular), EEG= electroencephalogram (C3-A2), Pepi= pressure at the level of the epiglottis, Pmask= pressure measured via nasal mask, Vt = tidal volume and flow measured via nasal mask and pneumotachograph. There was increased EMGgg activity during the apnoeic event, though it was not significant enough to restore flow without arousal. The arousal threshold is characterized using Pepi, and after arousal there is a large ventilatory response.

Table

Summary of OSA pathophysiological traits. The mechanisms that may contribute to these traits are highlighted as well as potential targeted treatments approaches. Possible genetic links to these traits are also included

OSA pathophysiology	Possible mechanism	Possible targeted treatment option	Genetic link
Compromised upper airway anatomy	Anatomically smaller airway, altered soft tissue	Surgery in selected cases	Bony facial features, postion of maxillae and madible are heritable
Decreased dilator muscle activity during sleep	Neurochemical alterations at sleep onset; UA trauma/oedema leading to neuoropathy/myopathy	Hypoglossal activation/ stimulation; pharmacotherapy in the future	Unknown
Decreased arousal threshold	Cannot recruit dilator muscle to open airway before arousal occurs	Hypnotic agents to subjects with low arousal thresholds and recruitable muscles	Unknown
Unstable ventilatory control (increased loop gain)	Increases oscillations from brain stem pattern generator, augment ventilatory response to arousal driving $PaCO_2$ below apnoea threshold	Oxygen; acetazolamide	Similar response to hypoxia and inspiratory resistance among relatives. SIDS and OSA co-segregate in families
Decreased lung volume	Increasing EELV improves respiratory mechanics possibly by increasing caudal traction on upper airway	Lung volume Augmentation; Cuirass; Negative extrathoracic pressure	Indirectly, obesity may cause decreased lung volume

EELV, End-expiratory lung volume; SIDS, sudden infant death syndrome; UA, upper airway