

# Obstructive sleep apnea: current perspectives

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**Abstract:** The prevalence of obstructive sleep apnea (OSA) continues to rise. So too do the health, safety, and economic consequences. On an individual level, the causes and consequences of OSA can vary substantially between patients. In recent years, four key contributors to OSA pathogenesis or “phenotypes” have been characterized. These include a narrow, crowded, or collapsible upper airway “anatomical compromise” and “non-anatomical” contributors such as ineffective pharyngeal dilator muscle function during sleep, a low threshold for arousal to airway narrowing during sleep, and unstable control of breathing (high loop gain). Each of these phenotypes is a target for therapy. This review summarizes the latest knowledge on the different contributors to OSA with a focus on measurement techniques including emerging clinical tools designed to facilitate translation of new cause-driven targeted approaches to treat OSA. The potential for some of the specific pathophysiological causes of OSA to drive some of the key symptoms and consequences of OSA is also highlighted.

**Keywords:** pathophysiology, sleep-disordered breathing, arousal, upper airway physiology, control of breathing, precision medicine

## Introduction

Obstructive sleep apnea (OSA) is an increasingly common, chronic, sleep-related breathing disorder.<sup>1–3</sup> OSA is characterized by periodic narrowing and obstruction of the pharyngeal airway during sleep. Untreated OSA is associated with long-term health consequences including cardiovascular disease,<sup>4,5</sup> metabolic disorders,<sup>6</sup> cognitive impairment,<sup>7</sup> and depression.<sup>8</sup> Common symptoms include excessive daytime sleepiness, fatigue, non-refreshing sleep, nocturia, morning headache, irritability, and memory loss.<sup>9,10</sup> Untreated OSA is also associated with lost productivity and workplace and motor vehicle accidents resulting in injury and fatality.<sup>11–13</sup> The costs of untreated OSA and sleep loss are substantial.<sup>14,15</sup> Recommended therapy can relieve symptoms<sup>16,17</sup> and reduce some of the associated sequelae.<sup>18,19</sup> However, many people with OSA struggle with the first-line therapy, continuous positive airway pressure (CPAP), for which adherence rates remain unacceptably low.<sup>20,21</sup> Non-CPAP therapies (e.g., oral appliance therapy and upper airway surgery) are beneficial in many cases but have variable and unpredictable efficacy.<sup>22–25</sup> Thus, new approaches to treat OSA are required.

Indeed, most people with OSA are undiagnosed and untreated.<sup>26–28</sup> In some cases, this may be attributed to, at least in part, a lack of awareness of the disorder.<sup>29</sup> Other potential barriers to seek treatment include stigma related to some of the features of the disease such as snoring, access to polysomnography (PSG) and diagnostic services

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(particularly in remote communities and in the developing world),<sup>27,29</sup> perceived lack of enthusiasm with existing treatment options, and, in some cases, concern that driving licenses will be revoked. In addition, primary care physicians may not be prompted to explore an early diagnosis of OSA. This is especially true if patients do not present with subjective sleepiness and the classic characteristics of a high body mass index. Symptoms such as fatigue or sleepiness may also be attributed to comorbid disease that is common in people with OSA.<sup>30</sup> However, we know that absence of subjective sleepiness does not rule out substantial sleep-disordered breathing and up to 50% of people with OSA are not obese.<sup>23,31</sup> Indeed, 25% of individuals with moderate OSA have neither subjective nor objective sleepiness.<sup>32,33</sup> Nonetheless, given the burden of disease, the shortcomings of existing diagnostic and treatment approaches, and the substantial health, safety, and economic consequences of untreated OSA, there is a pressing need to continue to raise awareness and develop new strategies to manage and treat this common chronic health condition.

There are multiple contributors to OSA.<sup>34,35</sup> Each contributor represents a therapeutic target.<sup>34,35</sup> While these new research findings offer hope for new therapies, identification of these new targets has not yet translated to new models of care for OSA.<sup>36</sup> However, there has been recent progress toward achieving this goal. For example, strategies to extract information from existing clinical PSG studies to help inform treatment decisions according to a cause-driven targeted therapy model for OSA have been developed.<sup>37–41</sup> In accordance with this objective, simple wakefulness upper airway and respiratory physiology tests may also be useful.<sup>42–45</sup> These concepts are the focus of the current review.

## Existing clinical measures of OSA

The gold standard method used to diagnose sleep-disordered breathing is a comprehensive in-laboratory PSG. The main outcome used to define OSA severity is the apnea-hypopnea index (AHI). This index represents the number of breathing stoppages (apneas) and periods of reduced airflow (hypopneas) lasting greater than 10 seconds that result in a brief awakening (arousal) or reduced oxygenation that occur per hour of sleep. While severity cutoffs vary, mild sleep apnea is typically defined as 5–15, moderate 15–30, and severe more than 30 respiratory events/h sleep.

While in-laboratory PSG is comprehensive, it is also labor intensive, time-consuming, and costly (see the study by Edwards et al<sup>46</sup> for a review). To facilitate the diagnosis process, home-monitoring technologies have emerged. These

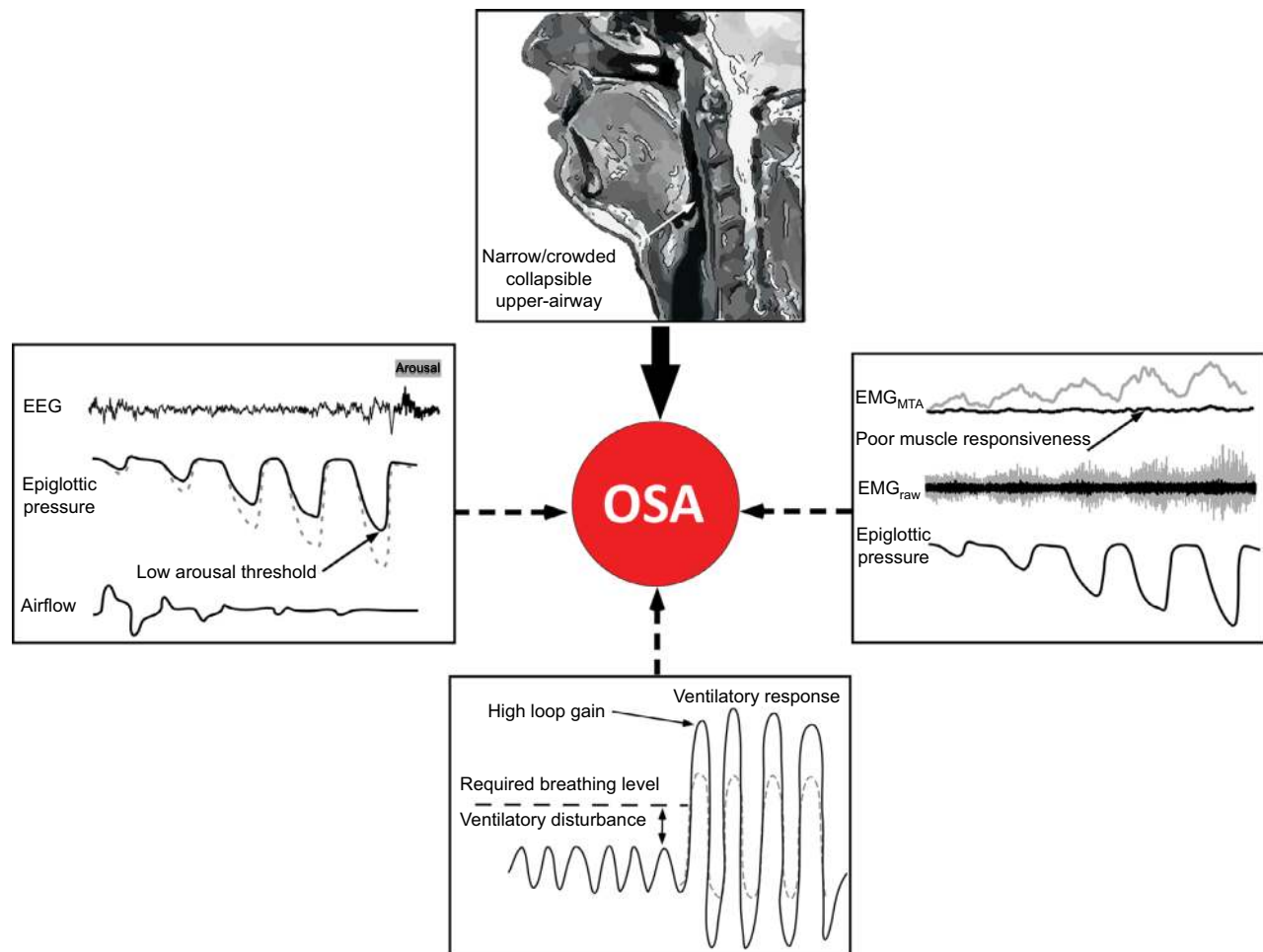
range from a replication of the same measurements used in the laboratory (a level 2 unattended study) to limited channel devices that focus on a few core signals (e.g., oxygen and an airflow sensor). These tend to be most useful for the detection of severe disease, provided patients do not have severe comorbidity.<sup>47–49</sup>

Despite the quantity of neurophysiological signals obtained during an overnight PSG, most of the data collected is ignored and treatment decisions rely heavily on the AHI. While the AHI remains a widely used measure of OSA severity clinically and for research purposes, it has several limitations. For example, a patient with very long respiratory events may experience substantial hypoxemia but have a relatively low AHI. Conversely, another patient may have more frequent events and therefore a much higher AHI, but minimal exposure to hypoxemia.<sup>50</sup> Thus, the effects of hypoxia from OSA and its adverse impact on the cardiovascular system in the patient with a low AHI may be more pronounced.<sup>51,52</sup> In addition, non-apneic respiratory events that do not meet the scoring criteria for a hypopnea are associated with heart rate changes and increased expiratory pharyngeal resistance.<sup>53</sup> Breathing disruptions that do not cause major hypoxemia are also associated with objective daytime sleepiness.<sup>54</sup> Furthermore, the total AHI correlates poorly with the key causes and consequences of the disease.<sup>35,55</sup> Conversely, recent studies indicate that REM sleep apnea may be more important in mediating insulin resistance and the cardiovascular consequences of OSA.<sup>56–59</sup> Thus, these examples highlight the heterogeneity in the various clinical manifestations of OSA and its consequences and some of the limitations with currently used diagnostic methods.

## OSA pathophysiology

Similar to the clinical heterogeneity, OSA pathogenesis is also multifactorial. There are “anatomical” and “non-anatomical” causes<sup>34,35,60</sup> (Figure 1). In recent years, the potential role that factors beyond pharyngeal anatomy and craniofacial structure play in OSA pathophysiology has been recognized. Indeed, OSA can develop due to multiple contributors, the combination of which likely varies substantially between patients. These concepts have been the focus of several recent review articles (e.g., studies by Eckert,<sup>34</sup> Carberry et al,<sup>36</sup> Edwards et al,<sup>61</sup> and Eckert and Wellman<sup>62</sup>) and are therefore only briefly summarized here.

Non-anatomical contributors include impaired pharyngeal dilator muscle function, premature awakening to mild airway narrowing (low respiratory arousal threshold), and unstable control of breathing (high loop gain<sup>3,34,35</sup>) (Figure 1).



**Figure 1** Schematic of the anatomical and non-anatomical causes of OSA.

**Notes:** Some degree of anatomical vulnerability is present in OSA. However, the extent of impairment varies widely between patients. The non-anatomical contributors, which are present in approximately 70% of OSA patients, play a key role in mediating the absence or presence of OSA. In the schematic, the gray tracings indicate the desired response, whereas the black tracings represent impairment in the non-anatomical trait. Refer to the text for further detail. Reprinted from Chest, Carberry JC, Amatoury J, Eckert DJ, Personalized management approach for OSA, Epub 2017 June 16, Copyright (2017), with permission from Elsevier.<sup>36</sup>

**Abbreviations:** EEG, electroencephalography; EMG, genioglossus electromyography; MTA, 100 ms moving time average of the rectified raw EMG signal; OSA, obstructive sleep apnea.

As highlighted in later sections, when combined with a pharyngeal airway that is susceptible to closure during sleep, impairment in one or more of these non-anatomical contributors can perpetuate OSA severity. Given that airway obstruction in OSA only occurs during sleep, the combination of an anatomical predisposition combined with state-dependent changes in non-anatomical contributors is crucial in driving this common disorder.<sup>34,35,63</sup>

## OSA is largely a sleep-dependent anatomical problem

As highlighted, OSA is a multifactorial disorder. However, some level of upper airway anatomical impairment is essential.<sup>34,35</sup> Thus, it is logical that most existing therapies for OSA aim to correct the anatomical problem. Imaging studies<sup>64–66</sup> have identified key pharyngeal anatomical abnormalities in

people with OSA. For example, a narrow pharyngeal airway, increased airway length, and certain pharyngeal lumen shapes are all associated with the propensity for pharyngeal collapse during sleep.<sup>67–69</sup> The upper airway can collapse at one or multiple sites.<sup>70</sup> The pharyngeal structures that can contribute to airway crowding and collapse include the dilator muscles such as genioglossus, soft palate, lateral pharyngeal walls, and the epiglottis. Obesity is an important risk factor.<sup>71</sup> Neck circumference is routinely measured in the clinic and has been used to help predict OSA risk.<sup>72,73</sup> Craniofacial morphology,<sup>74,75</sup> position of the hyoid bone,<sup>76</sup> airway surface tension,<sup>77</sup> tongue scalloping,<sup>78</sup> and tongue fat<sup>79</sup> are some of the factors associated with OSA risk and its severity. While these approaches have provided insight into OSA pathogenesis, limitations for clinical use include 1) high cost of imaging procedures and 2) awake static imaging provides limited

insight into the properties of a dynamic structure that closes involuntarily during sleep.

## Upper airway collapsibility

Pharyngeal critical closing pressure (Pcrit) is a well-established technique used to quantify upper airway collapsibility during sleep.<sup>80-82</sup> Pcrit has been used to describe differences in upper airway collapsibility across the sleep-disordered breathing spectrum (from snoring to OSA<sup>80</sup>). It is considered as the gold standard approach to quantify “functional anatomy” during sleep.<sup>34</sup> The Pcrit technique allows the pharyngeal airway to be examined under conditions of reduced,<sup>82</sup> although not absent,<sup>83</sup> neuromuscular input compared to wakefulness. Once a therapeutic CPAP level that prevents airway obstruction or narrowing is established, brief reductions (5 breaths) in the holding pressure are applied during stable sleep.<sup>70</sup> This procedure is repeated at different levels of mask pressure until airflow limitation and closure occurs. The pressure-flow relationship between peak inspiratory flow for flow-limited breaths and the corresponding mask pressure is compared. These values are then extrapolated to determine the “Pcrit”, the mask pressure at zero airflow. Within an individual, Pcrit measurements are stable over time (days to months).<sup>84</sup> However, factors such as weight gain over a longer period would be expected to increase airway collapsibility (Pcrit).<sup>85,86</sup>

On average, OSA patients tend to have Pcrit values near atmospheric pressure. This indicates that their airway closes at or near 0 cmH<sub>2</sub>O during sleep.<sup>35,76,86</sup> However, there is substantial variability in Pcrit in OSA and therefore anatomical vulnerability to pharyngeal collapse. Indeed, Pcrit can range from approximately -5 to greater than +5 cmH<sub>2</sub>O in OSA. A Pcrit at or near +5 cmH<sub>2</sub>O indicates a highly collapsible airway, whereas a sub-atmospheric Pcrit indicates a relatively stable upper airway as suction pressure is required to close the upper airway during sleep. OSA is very rare in people with Pcrit values less than -5 cmH<sub>2</sub>O.<sup>35,86</sup> However, within the sub-atmospheric range (0 to -5 cmH<sub>2</sub>O), there is considerable overlap in Pcrit between people with and without OSA. Indeed, approximately 20% of OSA patients have similar pharyngeal collapsibility during sleep compared to people without OSA.<sup>35</sup> In this group, the interaction between mild anatomical susceptibility and impairment in one or more of the non-anatomical causes of OSA is crucial in driving OSA pathogenesis.<sup>34,35</sup> These patients are more likely to benefit from targeted non-CPAP therapies compared to those with very high Pcrits.<sup>34,36</sup> Thus, given the key role that upper airway anatomy/collapsibility plays in driving OSA pathogenesis, a

simple measure of airway collapsibility would be invaluable to inform targeted treatment decisions. The problem, however, is that the Pcrit technique is not clinically viable as the protocol is technically challenging, somewhat invasive (requires CPAP and ideally a pharyngeal pressure catheter), time-consuming, and requires skilled personnel to collect and analyze the data.

## New simplified methods to estimate upper airway collapsibility

There has been recent progress toward development of simple and reliable methods to estimate the extent of anatomical/airway collapsibility contribution to OSA. The first technique involves an existing tool traditionally used to assess expiratory flow limitation in patients with chronic obstructive pulmonary disease.<sup>42</sup> Participants are fitted with a nasal breathing mask and brief (2 second) periods of negative pressure (-5 cmH<sub>2</sub>O) are delivered during early expiration.<sup>42</sup> This elicits a transient increase in expiratory airflow the extent to which is mediated, at least in part, by upper airway collapsibility/anatomy. The average response is quantified as the ratio between the exhaled volumes (during the first 0.2 seconds) for at least 4 breaths prior to the expiratory pressure application versus the expiratory pressure breaths for 10 replicate trials. An increase in this ratio suggests a collapsible airway. A modest relationship with Pcrit and other important anatomical components that contribute to OSA was detected.<sup>42</sup> Thus, this technique alone is unlikely to be helpful in informing treatment decisions, but if combined with other simple measures it may play a role.

Preliminary data from our group indicate that a 10–15 minute protocol in which brief pulses of suction are applied during early inspiration through a nasal mask during wakefulness correlates well with Pcrit.<sup>43</sup> The prescribed CPAP level from a routine CPAP titration study is also associated with passive Pcrit.<sup>37</sup> Thus, the therapeutic CPAP level may be useful in distinguishing patients with mildly versus highly collapsible upper airways.<sup>37</sup> Genta et al<sup>39</sup> have also recently demonstrated that analysis of the shape of the inspiratory flow curve during airflow limitation during sleep and the degree of negative effort dependence (extent to which the airway narrows during inspiration) can inform the site of upper airway collapse. This was determined using endoscopy to locate the site of collapse while simultaneously monitoring nasal airflow and pharyngeal pressures. Averaging multiple flow-limited breaths revealed characteristic flow patterns that were associated with different sites of airway narrowing/collapse.<sup>39</sup> In addition, simply quantifying peak flow during routine polysomnography has recently been shown to be associated

with active Pcrit (a measure that encompasses upper airway collapsibility and neuromuscular compensation<sup>40</sup>). Thus, there are several new promising approaches to estimate the extent of anatomical impairment in people with OSA. Given their relative simplicity, one or more of these approaches may be preferable compared to more invasive procedures such as drug-induced endoscopy, which is becoming increasingly used to help inform patient selection for upper airway surgery.<sup>87</sup>

## The upper airway muscles

The human pharynx is unique in that it lacks rigid bony support. Its predominant soft tissue structure enables it to change cross-sectional area with varying intraluminal pressures. However, depending on the dynamic balance of intraluminal pressure and neural drive to the upper airway dilator muscles, the human pharynx is vulnerable to collapse during sleep.<sup>88</sup> There are over 20 muscles in the upper airway. These are involved in respiratory and non-respiratory tasks (speech, mastication, swallowing, and breathing). A subset of these muscles plays a predominant role in airway stability during breathing.<sup>89</sup> In healthy individuals and people with OSA during wakefulness, activation of the upper airway dilator muscles is effective in opposing the collapsing pressures generated during inspiration. However, during sleep, state-dependent reductions in muscle activity when combined with anatomical susceptibility (narrow/crowded/collapsible airway) can induce airway collapse.<sup>88</sup> Thus, understanding the neural control of the airway muscles and their mechanical consequences is important for development of new treatments and preventative measures to improve upper airway function in OSA.

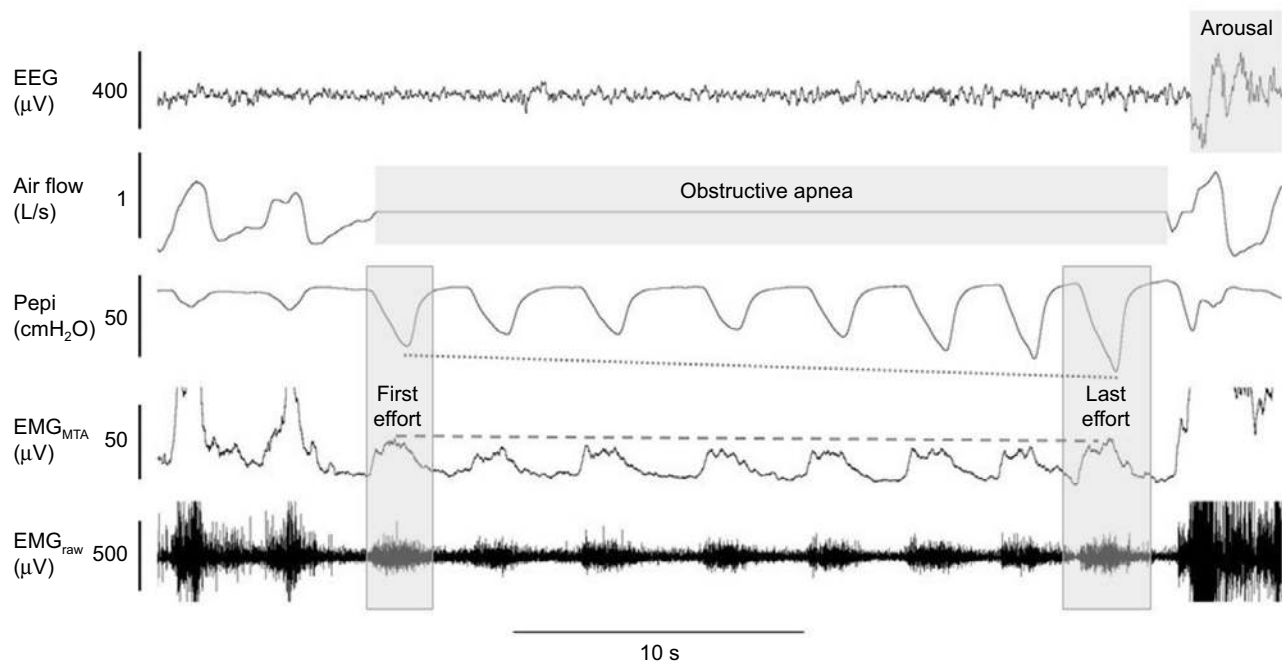
The upper airway muscles have complex patterns of neural activation that differ between muscles. For example, the genioglossus, the largest pharyngeal dilator muscle located at the base of the tongue, receives up to six different patterns of drive.<sup>90</sup> It receives central input from the brainstem (respiratory pattern generator neurons) and reflex input from pharyngeal mechanoreceptors and chemoreceptors. The summation of drive to genioglossus typically results in a phasic pattern of activation (i.e., more activity during inspiration and less during expiration, Figures 1–4). Genioglossus activity is reduced at sleep onset<sup>91</sup> and varies between sleep stages.<sup>83</sup> However the tensor palatini muscle (a palatal muscle) displays predominantly tonic (constant throughout the breathing cycle) patterns of activation.<sup>92</sup> It is less sensitive to small changes in pharyngeal pressure compared to genioglossus but can be activated in a similar manner with larger transient pressure swings<sup>93</sup> and is sensitive to sleep state

but has minimal change across sleep stages in the absence of upper airway resistance.<sup>83</sup> The combinations of a loss in central drive and reflex input to the upper airway muscles during sleep are thought to be important contributors to OSA pathogenesis.<sup>94,95</sup> Similarly, the ability to increase reflex drive to airway narrowing during sleep is important in OSA pathogenesis.<sup>35,96,97</sup> Indeed, approximately 30% of OSA patients have poor genioglossus muscle responsiveness to airway narrowing during sleep<sup>35</sup> (Figure 2). Many patients have a high recruitment threshold to respiratory stimuli during sleep that is not reached without awakening from sleep (arousal).<sup>96</sup> Conversely, others are able to restore airflow during sleep via pharyngeal muscle recruitment without arousal (Figure 3). In addition, enhanced muscle responsiveness can protect certain obese individuals from developing OSA despite their anatomical compromise.<sup>98</sup> Thus, the combination of non-anatomical and anatomical compromise is crucial in preventing or promoting OSA.

In addition, recent findings suggest a mismatch between central neural drive to the genioglossus muscle and the mechanical response of the muscles in OSA patients.<sup>99</sup> Indeed, in healthy individuals, dynamic magnetic resonance imaging shows anterior movement of this fan-shaped muscle during inspiration and increased cross-sectional area (CSA) of the pharynx.<sup>100</sup> However, tongue movement patterns during quiet breathing vary in people with OSA.<sup>101</sup> Some patients have counterproductive motion characterized by anterior motion at the base of the tongue followed by airway narrowing at the level of the soft palate, while others have little to no movement during inspiration.<sup>101</sup> These patterns of movement are dependent, at least in part, on OSA severity whereby minimal movement is most common in severe OSA.<sup>101</sup> Compensatory mechanisms in healthy individuals who have a narrow airway CSA compared to controls display larger anterior movement of the tongue during inspiration.<sup>102</sup> Accordingly, breathing stability is associated with greater genioglossus activity.<sup>103</sup> However, increased genioglossus activity is sometimes insufficient to re-open the airway (Figure 4). Thus, the contribution of the other upper airway muscles may also play a contributing role.<sup>104</sup> How the various components of upper airway muscle function change over time is unknown. However, increased weight gain over time and fat accumulation in the tongue are predicted to worsen upper airway motion.<sup>79</sup>

## Treatments to target the upper airway muscles

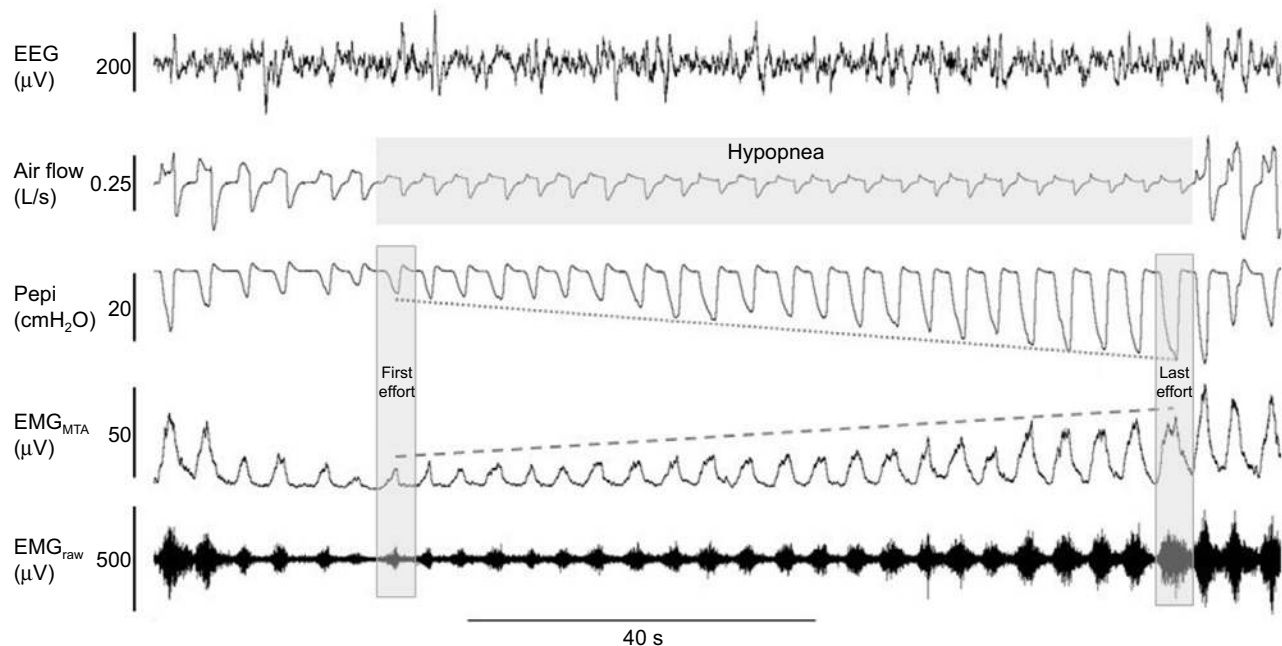
One approach to activate the upper airway muscles during sleep is to deliver current to the muscles via direct stimulation



**Figure 2** Example of minimal genioglossus muscle responsiveness.

**Notes:** In this example of a naturally occurring apnea, despite clear phasic activation of the genioglossus muscle (as shown in the raw and MTA genioglossus EMG channels), there is minimal activation of genioglossus during the respiratory event. This is despite substantial increasing negative epiglottic pressure (Pepi) swings from the first to last effort (last effort nadir epiglottic pressure = arousal threshold). It is only when cortical arousal occurs (as shown in the EEG channel) that major genioglossus activation occurs (signal clipped in this example) and airflow is restored.

**Abbreviations:** EEG, electroencephalography; EMG, genioglossus electromyography; MTA, 100 ms moving time average of the rectified raw EMG signal.



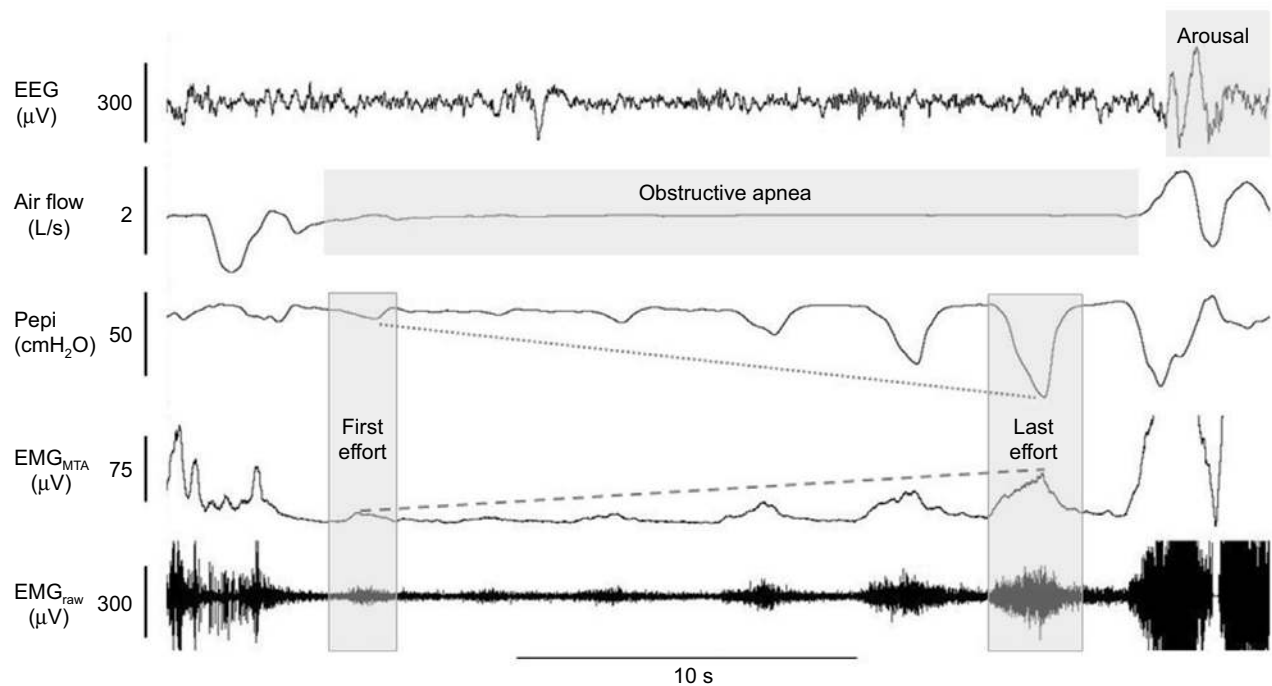
**Figure 3** Example of robust genioglossus muscle responsiveness and restoration of airflow without cortical arousal.

**Notes:** In contrast to the example in Figure 2, in this example of a naturally occurring hypopnea, there is robust activation of the genioglossus muscle (as shown in the raw and MTA genioglossus EMG channels), to increasing negative epiglottic pressure (Pepi) swings from the first to last effort which ultimately results in recovery of airflow without cortical arousal.

**Abbreviations:** EEG, electroencephalogram; EMG, genioglossus electromyography; MTA, 100 ms moving time average of the rectified raw EMG signal.

or via stimulation of the hypoglossal nerve. Clinically, this is achieved via surgical implantation of a stimulation device connected to a cuff placed around the nerve.<sup>105</sup> Mechanistic

studies have also used fine-wire electrodes or non-invasive methods such as transcutaneous electrodes (see recent review to compare different methods<sup>106</sup>). Improvements in



**Figure 4** Example of robust genioglossus muscle responsiveness without restoration of airflow.

**Notes:** In contrast to the example in Figure 3, in this example of a naturally occurring apnea, there is robust activation of the genioglossus muscle (as shown in the raw and MTA genioglossus EMG channels) to increasing negative epiglottic pressure (Pepi) swings from the first to last effort (last effort nadir epiglottic pressure = arousal threshold). However, despite substantial genioglossus muscle activation during the apnea, it is insufficient to restore airflow, which only occurs with cortical arousal (as shown in the EEG channel). The genioglossus signal is clipped in this example when airflow is restored with arousal.

**Abbreviations:** EEG, electroencephalogram; EMG, genioglossus electromyography; MTA, 100 ms moving time average of the rectified raw EMG signal.

inspiratory airflow, AHI, apnea duration, oxygen saturation, arousal index, sleep architecture, and excessive daytime sleepiness have all been reported to varying degrees using these methods.<sup>107–111</sup> Clinical trial follow-up studies show long-term sustained reductions in AHI (~50–66%).<sup>111–114</sup> However, it is difficult to predict responders. The STAR trial used endoscopy for pre-screening to eliminate patients with concentric airway collapse, which may have increased the response rate to therapy.<sup>105</sup> However, one-third of patients were still classified as non-responders.<sup>105</sup> Thus, other factors such as airway shape and  $P_{crit}$  are also likely to be important considerations to optimize treatment response rates.<sup>105,110</sup>

To date, attempts to develop pharmacotherapy to increase upper airway muscle activity to treat OSA have not been successful. Targets have included serotonergic, noradrenergic and GABAergic systems, as well as potassium channels (for reviews see).<sup>115,116</sup> However, recent studies with the tricyclic antidepressant desipramine which has strong noradrenergic, mild antimuscarinic, and mild serotonergic effects, have shown preservation of sleep-related reductions in genioglossus activity.<sup>117</sup> Desipramine also yields improvements in airway collapsibility and OSA severity in patients with poor muscle responsiveness.<sup>118</sup> Thus, this combined approach may be

superior to single system targets.<sup>115,119–121</sup> Interestingly, the hypnotic zolpidem (which acts on the GABAergic system) shows potential to increase pharyngeal muscle responsiveness during airway narrowing without impairing the other key causes of OSA.<sup>122</sup> Designer Receptors Exclusively Activated by Designer Drugs that allow for selective targeting of a group of neurons via introduction of an engineered macromolecule (designer receptor) with viral vectors that can be activated with a specific drug (designer drug) have also recently been tested in animal models with the objective to increase pharyngeal muscle activity during sleep.<sup>123,124</sup> These exciting findings demonstrate lasting increases in genioglossus activity and offer promise that these new concepts will ultimately translate to humans.

Other strategies to improve pharyngeal muscle function include training modalities. Indeed, regular didgeridoo playing and oropharyngeal exercises can reduce snoring and OSA severity (~50% reduction in AHI) and daytime sleepiness.<sup>125–128</sup> However, the mechanisms are largely unknown. No studies have investigated upper airway muscle tone or muscle properties pre-training versus post-training. Longitudinal follow-up studies are also lacking. Understanding the mechanisms may help to inform which OSA phenotypes are most likely to respond to this form of therapy.

## Prediction tools and simplified methods to estimate pharyngeal muscle function

Identification of patients who have poor pharyngeal muscle function may facilitate development of targeted therapies directed toward this trait<sup>118</sup> and improve treatment success rates with existing therapies (e.g., hypoglossal nerve stimulation). However, gold standard methodology to quantify pharyngeal muscle activity is complex, invasive (fine-wire electrodes inserted directly into the muscle), requires specialized personnel and equipment, and is time-consuming.<sup>34</sup> There are no simplified tools to estimate pharyngeal muscle function to identify people with this clinical phenotype accurately. However, while multiple variables impact inspiratory flow during sleep, mean peak inspiratory airflow during airflow limitation appears to be a good surrogate for active Pcrit, a measure that incorporates both anatomical and neuromuscular components.<sup>40</sup> Thus, if this approach proves useful to predict treatment outcomes, automated signal processing algorithms based on routine PSG data could be implemented.<sup>40</sup> Nonetheless, additional practical tools to determine pharyngeal muscle function are urgently required in order to advance personalized treatment approaches that target the upper airway muscles.

## Respiratory arousal threshold

The role of the respiratory arousal threshold in OSA pathogenesis has been described in detail.<sup>129</sup> Accordingly, these concepts are outlined only briefly here. Historically, given that most respiratory events are associated with a cortical arousal, arousals were considered crucial to reopen the upper airway following a respiratory event in OSA.<sup>130,131</sup> However, approximately 20% of respiratory events cease without cortical arousal and an additional 20% occur after the upper airway has already reopened and airflow has been restored.<sup>129,132–134</sup> Indeed, 75% of adults with OSA have respiratory events that terminate without an arousal or the arousal occurs following airway reopening at some stage of the night.<sup>132</sup> Thus, airway reopening can occur without arousal. Rather, continual unnecessary arousals can worsen OSA and contribute to OSA pathophysiology.<sup>129,132</sup> Specifically, repetitive arousals can perpetuate blood-gas disturbances and cause sleep fragmentation to promote cyclical breathing and prevent establishment and maintenance of more stable, deeper stages of sleep.<sup>135–138</sup>

Numerous respiratory stimuli can contribute to arousal from sleep during a respiratory event.<sup>129,139–142</sup> Increased respiratory effort due to a narrowed pharyngeal airway increases negative intrathoracic pressure. Although the amount of negative intrathoracic pressure generated can

vary greatly between individuals and in different stages of sleep,<sup>35,132,143–147</sup> the magnitude of negative pressure required to cause an arousal from sleep is relatively constant within an individual.<sup>147–149</sup> This is the case regardless of whether the respiratory disturbance is caused by hypoxia, hypercapnia, or respiratory loading.<sup>147</sup>

Accordingly, the gold standard method to quantify the threshold for arousal to respiratory stimuli requires an epiglottic or esophageal pressure catheter combined with PSG recording equipment. Specifically, the respiratory arousal threshold is the nadir pressure immediately prior to cortical arousal (Figures 1, 2, and 4). The respiratory arousal threshold is quantified by averaging multiple pressure values throughout the night to an experimental intervention designed to cause airway narrowing or activate respiratory afferents<sup>35,147</sup> or during naturally occurring respiratory events.<sup>144,145</sup>

In people with OSA who require large intrathoracic pressure swings to cause an arousal (i.e., patients with high respiratory arousal thresholds  $\leq 25$  cmH<sub>2</sub>O), respiratory events are often prolonged, particularly if these patients also have poor upper airway muscle responsiveness.<sup>129</sup> Thus, in the absence of neuromuscular compensation, arousal from sleep and reintroduction of wakefulness drive can act as a last line of defense to facilitate rapid reopening of the airway to re-establish airflow and normalize blood-gas levels in these individuals.<sup>129,130,150</sup> The consequences of OSA such as sleep deprivation increase, while CPAP therapy decreases the respiratory arousal threshold.<sup>151,152</sup> Nonetheless, approximately 30–50% of OSA patients wake to relatively small intrathoracic/epiglottic pressure swings (i.e., patients with low respiratory arousal thresholds  $\geq -15$  cmH<sub>2</sub>O).<sup>35,38,129,145</sup> In these patients, given that the stimuli for arousal are the same as the stimuli required to recruit the pharyngeal dilator muscles (i.e., blood gas changes and negative pressure swings), premature arousal limits the opportunity for neuromuscular compensation mechanisms to overcome airway narrowing and stabilize breathing.<sup>132</sup> Frequent arousals can also cause sleep fragmentation and sleep instability, prevent deeper stages of sleep, and perpetuate unstable breathing.<sup>132,142</sup> Thus, strategies to reduce arousals in these patients may allow for more stable breathing during sleep.

## Treatments to target the respiratory arousal threshold

Given the abovementioned rationale, the potential therapeutic role of hypnotics to treat OSA in patients with a low respiratory arousal threshold phenotype has been an area



of recent research focus.<sup>150</sup> This strategy requires a careful targeted approach to optimize benefit in those with the desired phenotype and avoid harm in those with high arousal thresholds. In particular, the selected agent to increase the threshold for arousal to respiratory stimuli must do so without impairment in pharyngeal muscle activity. Apart from an early wakefulness benzodiazepine study,<sup>22</sup> subsequent studies during sleep have not shown systematic reductions in pharyngeal muscle activity or responsiveness to negative pharyngeal pressure with common doses of zopiclone,<sup>96,144</sup> trazodone,<sup>153</sup> temazepam,<sup>122</sup> or zolpidem.<sup>122</sup> While a recent study found more variable effects on genioglossus muscle responsiveness with temazepam, paradoxically, on average, zolpidem increased muscle responsiveness 3-fold in people with and without OSA.<sup>122</sup>

The other concern with hypnotic use in OSA is prolongation of respiratory events and worsening hypoxemia due to blunted arousal responses in those individuals with a high threshold for respiratory arousal. Indeed, this can occur with high doses or in obese patients with very severe disease.<sup>129</sup> By contrast, the hypnotics eszopiclone,<sup>145</sup> zopiclone,<sup>22</sup> and trazodone<sup>154</sup> can reduce OSA severity as measured by the AHI without worsening hypoxemia. In the eszopiclone study,<sup>145</sup> reductions in AHI occurred invariably in those with a low arousal threshold phenotype. The number of arousals per hour of sleep also decreased.<sup>145</sup> Given the contrasting effects of hypnotics in OSA, screening tools to distinguish between patients with low and high respiratory arousal thresholds and to determine who will benefit versus be susceptible to harm are important.

## Prediction tools and simplified methods to estimate the respiratory arousal threshold

The gold standard approach to quantify the respiratory arousal threshold is impractical for routine clinical use as it is time-consuming, costly, and somewhat invasive (requires an airway pressure catheter). Preliminary findings indicate that respiratory sensation to inspiratory loading during wakefulness is related to the respiratory arousal threshold during sleep.<sup>155</sup> Edwards et al have developed a simple tool to estimate the respiratory arousal threshold with high sensitivity and specificity based on three measures from a standard overnight PSG (AHI, nadir oxygen saturation, and the apnea to hypopnea ratio).<sup>38</sup> Thus, while prospective intervention studies are required, this simple approach could easily be implemented in the clinical setting to inform treatment

decisions. Given that over 40% of OSA patients may also have insomnia,<sup>156–158</sup> simple accurate tools to determine which OSA patients will benefit versus those at risk of harm with hypnotics would be invaluable.

## Loop gain

Loop gain is a term used to describe the stability of a feedback control system. In the context of respiratory physiology, loop gain is the ventilatory response to ventilatory disturbance ratio. It comprises three principal components: 1) plant gain (i.e., tissues, blood, and lungs where CO<sub>2</sub> is stored) and 2) delays in circulation (i.e., time it takes for a change in CO<sub>2</sub> to mix with the existing blood to arrive and be detected by the chemoreceptors) and 3) controller gain (i.e., chemosensitivity). Any medical condition that modifies one or more of these components (e.g., heart failure) will alter loop gain.<sup>34</sup> Components of OSA such as intermittent hypoxia can also alter respiratory control.<sup>159</sup> People with high loop gain have exaggerated ventilatory responses to minimal changes in CO<sub>2</sub>. This is a marker of an unstable control system. This can be reduced with CPAP therapy.<sup>160</sup> On the other hand, those with extremely low loop gain often experience hypoventilation during sleep, as is the case in people with obesity hypoventilation syndrome.<sup>34</sup>

In their landmark study using proportional assist ventilation to induce breathing oscillations during sleep after the airway was stabilized with CPAP, Younes et al showed that severe OSA patients have high loop gain.<sup>138</sup> Subsequent studies confirmed that many people with OSA have high loop gain.<sup>35,161</sup> When combined with even a modest impairment in upper airway anatomy, high loop gain can drive OSA pathogenesis.<sup>35,161</sup> Similar to the other phenotypic traits, loop gain can be quantified using transient reductions in CPAP during sleep to create a disturbance to breathing.<sup>161,162</sup> Rapid reintroduction of CPAP is then applied so that the ventilatory response (overshoot) can be quantified (using a breathing mask and pneumotachograph) to calculate loop gain. This procedure is repeated as many times as possible throughout the night. Loop gain is then calculated as the ventilatory response divided by the ventilatory disturbance ratio after scaling for the different levels of ventilatory disturbances presented.<sup>161,162</sup> This technique results in a negative number such that more negative numbers reflect higher loop gain.<sup>162</sup> Approximately one-third of OSA patients have high loop gain (<-5) which indicates a >5 L/min increase in minute ventilation in response to 1 L/min reduction in minute ventilation.<sup>35</sup>

## Treatments to target loop gain and simplified methods to estimate loop gain

O<sub>2</sub> therapy reduces loop gain and OSA severity in people with high loop gain.<sup>163</sup> Carbonic anhydrase inhibitors such as acetazolamide also reduce loop gain by approximately 40% and OSA severity.<sup>164</sup> Similarly, zonisamide reduces OSA severity.<sup>24</sup> In addition, stabilization of CO<sub>2</sub> and hypercapnia can prevent hypoventilation and unstable respiratory control during sleep in OSA.<sup>165</sup> Strategies that combine O<sub>2</sub> therapy to reduce loop gain with a hypnotic to increase the arousal threshold can yield major reductions in OSA severity.<sup>146</sup> In addition, recent studies from the Mateika group indicate that several of the key contributors to OSA such as airway collapsibility, arousal threshold, and respiratory control are influenced by circadian phase.<sup>166–168</sup> Thus, novel strategies that target the circadian system may have therapeutic potential in OSA.

The current approaches to quantify loop gain during sleep require experienced personnel to perform CPAP manipulations and analyze the data. However, Terrill et al have developed an analysis approach that uses the nasal pressure signal from a standard PSG to estimate loop gain.<sup>41</sup> This approach has been used to explain and predict changes to a range of interventions in OSA.<sup>30,47,146</sup> Wakefulness tests of respiratory control may also be helpful in estimating responses to pharmacotherapies.<sup>44,45</sup>

## Potential links between phenotypic traits, treatment, and health consequences

In addition to the role that the phenotypic traits play in contributing to OSA pathogenesis, the traits may also provide insight into disease consequences and physiological reasons for treatment failure. For example, a low arousal threshold trait may be a physiological contributor to poor CPAP adherence and compliance.<sup>31</sup> A low arousal threshold trait and its consequences such as sleep fragmentation and frequent hypopneas with minimal changes in oxygenation may be a marker for cognitive impairment and daytime sleepiness.<sup>54,169</sup> Similarly, patients who tend to have more “intense” arousals, which appear to be an inherent trait,<sup>47,170</sup> may experience more daytime sleepiness than those who do not. People who have OSA that is driven by high loop gain may be more vulnerable to the cardiovascular consequences of OSA. Conversely, strategies that target certain components of respiratory control such as mild intermittent hypoxia to elicit respiratory plasticity may help improve CPAP compliance and potentially also directly target the autonomic, cardiovascular, neurocognitive, and metabolic systems.<sup>171,172</sup> While possible links between the phenotypic traits and specific disease consequences have

not yet been investigated, emergence of simplified tools to estimate the traits will enable these theoretical concepts to be tested systematically in cohort studies.

## Conclusion

Characterization of the different causes or phenotypes of OSA in recent years has provided new pathways for targeted therapy. New simplified approaches to estimate each of the key causes of OSA have recently been developed. While more work is required, particularly directed toward the impaired pharyngeal muscle trait, these new tools offer promise for the translation of detailed phenotyping concepts to the clinic. Identification of the traits may also provide insight in to which patients are more likely to develop specific disease consequences.

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