ABSTRACT
Obstructive sleep apnea (OSA) has multiple underlying mechanisms which vary across patients. In afflicted patients, the degree of abnormality in pharyngeal anatomy, dilator muscle function, ventilatory control instability etc is highly variable. In patients with anatomical compromise at the velopharynx, robust responses to palatal surgery would be predicted, whereas other patients may have no major improvement if the primary abnormality were elsewhere. Similarly, measures to influence ventilatory control such as oxygen or acetazolamide may yield major improvements, but only for patients with unstable ventilatory control. Further research into treatment of OSA based on underlying mechanism is required.

Keywords: apnea, future, lung, respiration, sleep, therapy.

RESUMO
A apnéia obstrutiva do sono possui diversos se dá por meio de diversos mecanismos, os quais variam entre pacientes. Entre os portadores desta condição, o grau de anormalidade na anatomia da faringe, função muscular, instabilidade no controle ventilatório, etc, são altamente variáveis. Em pacientes com comprometimento anatômico na velofaringe pode-se prever uma resposta robusta à cirurgia palatal, ao passo que outros pacientes podem não apresentar benefícios se a anormalidade primária for em outra região. De modo semelhante, medidas com efeito sobre o controle ventilatório, como oxigênio e acetazolamida podem resultar em melhores efeitos, mas apenas em pacientes com controle ventilatório instável. Mais pesquisas sobre o tratamento da apnéia obstrutiva do sono sob uma perspectiva mecanicista são necessários.

Descritores: apnéia, futuro, palmao, respiração, sono, terapia.

INTRODUCTION
Obstructive sleep apnea (OSA) is a very common disease with major neurocognitive and cardiovascular consequences. OSA with daytime symptoms is said to occur in 4% of North American men and 2% of North American women(1). However, considerable data suggest that these figures may be underestimates. The classic paper reporting these figures was from 1993, however obesity, the primary risk factor for OSA, is considerably more common than it was 20 years ago(2). In addition, technology has improved, including the use of nasal pressure to detect reductions in airflow(3,4), such that the 1993 figures would be higher if repeated today using modern technology(5). Moreover, the reported figures were based on daytime symptoms such as sleepiness. However, two lines of logic suggest that limiting the definition based on daytime sleepiness may be problematic. Many patients have symptoms such as fatigue, non-restorative sleep, disrupted sleep etc. without daytime sleepiness per se(6).

Thus, symptomatic disease is underestimated by the use of daytime sleepiness and many patients feel considerably better with treatment even though they are often inappropriately classified as ‘asymptomatic’(7). Given that many OSA patients are at risk of cardiometabolic consequences, the presence or absence of daytime sleepiness may not be relevant in terms of defining disease risk. A carefully performed epidemiological study from São Paulo has suggested a disease prevalence of 33% which may be a more realistic estimate than the previously reported figures from Young et al.(6). However, therapeutic data are lacking which will be critical to defining the ‘normal’ values and thus the threshold of disease required to define important OSA.

Despite the large burden of disease, therapy for OSA remains unsatisfactory. Nasal CPAP (continuous positive airway pressure) is the treatment of choice for OSA based on recent randomized trials(7). However, patients are often intolerant of CPAP and thus adherence to therapy can be a major issue(8). In addition, many patients avoid the diagnosis of OSA in an effort to avoid the eventual treatment with CPAP. Data also support the notion that a large number of patients are lost to followup, presumably in an effort to avoid CPAP therapy(9). Thus, despite its considerable efficacy, the effectiveness of CPAP is limited by adherence. Adherence can be improved with intensive support and patient education, and thus efforts to optimize outcome of CPAP-treated patients are recommended(10,11). Alternative therapies to OSA include oral appliances and upper airway surgery although both of these suffer from variable efficacy and poor ability to predict patients who will ultimately respond to therapy(12,13). Thus, new therapies for OSA are desirable(14).

Based on ongoing pathophysiological investigation, an emerging concept is one of individualized therapy based on underlying mechanism(15). The traditional view of OSA pathogenesis suggested that OSA patients have...
anatomical compromise, but were able to maintain pharyngeal airway patency during wakefulness through compensatory reflex mechanisms which increase the activity of pharyngeal dilator muscles including the genioglossus (the major substance of the tongue)[17]. However, with the onset of sleep, there is an attenuation in protective reflexes[18], leading to a fall in pharyngeal dilator muscle activation yielding pharyngeal collapse in those anatomically vulnerable[17,18]. Based on more recent data, however, each of these factors is highly variable across a population with OSA. Some OSA patients have severe anatomical compromise[19], whereas others have reasonably normal upper airway mechanics[20]. In addition, the responsiveness of pharyngeal dilator muscles during sleep is highly variable, with some patients having robust response to physiological stimuli whereas others have no major response[21]. In addition, measures of ventilatory control (so called loop gain) are also quite variable in OSA[22-27]. That is, some OSA patients are prone to ventilatory instability (high loop gain) whereas other patients have intrinsically stable control of breathing (low loop gain). Thus, the mechanisms underlying apnea are highly variable. As such, a ‘one size fits all’ therapeutic strategy is unlikely to be fruitful. For example, uvulopalatopharyngoplasty would be unlikely to be successful in patients who lack velopharyngeal compromise[28,29]. Similarly, a theoretical drug which could augment pharyngeal dilator muscle responsiveness may be helpful to some patients but theoretically deleterious in other patients[30]. These data suggest that an individualized approach to therapy using principles of personalized medicine may be worthwhile. Agents which stabilize ventilatory control appear to be effective in a definable subset of OSA patients who have ventilatory control instability[31]. Further, upper airway surgery is quite helpful in some patients but completely ineffective in others based on the anatomical characteristics of the individual undergoing a given procedure.

Using finite element analysis techniques, we have been developing a computational model to allow manipulations in anatomical features without the need for human experiments which would be regarded as unethical[12,31,32]. As such, we can compare the impact of various anatomical manipulations on the mechanics of the pharyngeal airway e.g. mandible advancement vs. uvula resection using the characteristics of an individual patient via magnetic resonance imaging and physiological measurements. This approach requires further validation, but the concept that the impact of various anatomical manipulations can be predicted a priori has precedent in neurosurgery and other areas[33]. In theory, the patients who are likely to fail uvulopalatopharyngoplasty (UPPP) could be identified ahead of time such that a different surgery or an oral appliance could be offered to such a patient rather than undergoing an ineffective procedure. On the other hand, patients likely to experience major benefit from such a procedure could be identified and targeted to optimize patient outcome.

PHARYNGEAL DILATOR MUSCLE CONTROL

The upper airway dilator muscles include the genioglossus and the tensor palatini. The GG is considered a major phasic muscle, as it bursts in activity with each inspiration[34]. The tensor palatini, on the other hand, has tonic activity, as it has constant activity throughout the respiratory cycle. These muscles can respond to respiratory stimuli during wakefulness, including sub-atmospheric pressure (negative pressure) and chemoreceptors (CO_2)[21,35,37]; however, their responsiveness during sleep is more variable. Thus some patients can defend pharyngeal airway patency during sleep, whereas others exhibit minimal ability to activate pharyngeal dilator muscles during sleep. In patients with minimal responsiveness of these muscles, arousal is generally required to restore airway patency, whereas patients with muscle responsiveness can activate muscles during stable sleep and allow a stable pharyngeal airway without the need for repetitive arousal[38-40]. As emphasized by Younes and others, most OSA patients have some periods of stable breathing. Jordan et al. determined that these stable periods are associated with elevated activity in the genioglossus muscle, whereas no other mechanism was capable of stabilizing breathing spontaneously. These data suggest that the genioglossus is both necessary and sufficient to stabilize breathing during stable sleep. Physiological mechanisms underlying genioglossus activation are likely to involve some combination of carbon dioxide and negative intrapharyngeal pressure[41]. Thus, a therapeutic target exists whereby robust activation of the genioglossus muscle would be predicted to be an effective therapy for OSA in selected individuals.

Using rat models, Chamberlin et al. have recently defined the neural circuitry underlying the activation of the genioglossus in response to negative intrapharyngeal pressure. The peri-olbe region of the medulla appears to be particularly critical for mediating the so-called negative pressure reflex. The local injection of muscimol, a non-specific inhibitor of neuronal activity via GABA-ergic mechanisms, can effectively eliminate the negative pressure reflex in rats suggesting that this region may be a therapeutic target for those patients with deficient reflexes. Kubin has shown heavy cholinergic staining among neurons in this medullary region suggesting that acetylcholine may be a potential therapeutic target for selected OSA patients. Indeed some clinical data have shown efficacy to cholinesterase inhibitor drugs in OSA, although the mechanism of action remains unknown[42]. In theory, cholinergic agents might improve the responsiveness of the negative pressure reflex which could improve OSA in selected patients. Similarly, hypoglossal nerve stimulation is now being studied by industry which may be beneficial for a subset of OSA patients.

AROUSAL THRESHOLD

The arousal threshold describes the propensity to awaken from sleep[43]. Some individuals have a low arousal threshold (easy to wake up) whereas others have a high arousal threshold (hard to wake up). Individuals who
wake up prematurely may develop repetitive apnea due to insufficient time for upper airway muscles to respond to physiological stimuli (such as CO₂ and negative pressure) [46]. On the other hand, people with a high arousal threshold may develop profound hypoxemia and hypercapnia prior to arousal. As such, the arousal threshold is often regarded as a 'double edged sword' since efforts to raise the arousal threshold would be predicted to improve breathing in some individuals but could be theoretically deleterious in others [47].

Agents to manipulate the arousal threshold such as sedative hypnotics are commonly used, but the ideal agent would be one that avoided skeletal muscle relaxation as would occur with alcohol or a benzodiazepine [48]. Heinzer et al. [47] have shown increases in the arousal threshold, particularly to chemoceptive stimuli using trazodone, although its impact on sleep apnea severity remains unknown [49]. Eckert et al. [50] have reported a randomized double blind, placebo-controlled study using eszopiclone (Lunesta) with improvements in the apnea hypopnea index observed as compared to placebo. Such strategies have not yielded complete resolution of sleep apnea, emphasizing the need for multiple strategies (e.g. combination therapy) to eliminate apnea. Efforts to define the central mechanisms underlying arousal and its various components may also allow the targeting of some components of arousal (e.g. respiratory) without the concomitant deleterious effects (e.g. cortical).

### LOOP GAIN

Loop gain is an engineering term which is used to define the instability in a negative feedback control system [51]. In the case of ventilation, a high loop gain describes a situation prone to ventilatory oscillations whereas a low loop gain defines a more stable breathing pattern. A high loop gain system would have marked fluctuations in carbon dioxide as would occur in Cheyne Stokes breathing, common in patients with congestive heart failure [52]. Although ventilatory control is known to be important in central apnea, its importance in OSA has only more recently been emphasized [27]. Some OSA patients have elevated loop gain such that oscillations in output from the central pattern generator occur with CO₂ fluctuations. Given that the pattern generator gives output to both the diaphragm and to the upper airway muscles, one would predict pharyngeal collapse when central output to the upper airway reaches its nadir in those who are anatomically predisposed [53]. Indeed efforts to stabilize ventilation (using oxygen or acetazolamide) are effective in lowering the apnea hypopnea index in selected individuals [50]. In patients with marked anatomical abnormality, ventilatory control may be less important since repetitive pharyngeal collapse would occur on a biomechanical basis. On the other hand, patients who are anatomically protected from OSA would have minimal impact from ventilatory control since oscillation of CPG output would be irrelevant in those lacking anatomical substrate for collapse. Patients with anatomical characteristics considered intermediate (neither protected nor markedly susceptible) may be those impacted by instability in ventilatory control [24]. As such, definable patients exist in whom manipulation of ventilatory control should be beneficial.

### LUNG VOLUME

End-expiratory lung volume (EELV) has an effect on upper airway patency [54,56]. Increases in end-expiratory lung volume have a tethering effect on the upper airway, whereas decreases in end-expiratory lung volume make the pharyngeal airway more susceptible to collapse. Manipulations in end-expiratory lung volume can be achieved by varying extrathoracic pressure which does influence pharyngeal patency and sleep apnea severity [57]. Other techniques to influence EELV either pharmacologically or electrically have not been systematically studied, although a subset of patients is likely to benefit from such approaches.

### BRAINSTEM NEUROCHEMISTRY

The hypoglossal motor nucleus and the motor branch of the trigeminal provide output to the critical upper airway muscles [58-60]. Considerable efforts have been ongoing to define the neurochemistry of these brain stem regions. Numerous nuclei project monosynaptically to the hypoglossal motor nucleus including raphe neurons (serotonergic), LDT/PPT (lateral dorsal tegmental and pediculo pontine tegmental cholinergic), locus ceruleus (adrnergic) and hypothalamic regions (orexinergic and histaminergic). Thus, various targets exist in these state dependent neuromodulatory systems which could theoretically augment hypoglossal output during stable sleep. The pharmacology of these regions is complex based on numerous receptor subtypes throughout the brain as well as systemically, but an approach to hypoglossal augmentation exists, which could benefit a subset of OSA patients.

### SUMMARY

OSA is an important but complex disease. The pathophysiology of this condition is being elucidated, with considerable evidence suggesting highly variable mechanisms underlying disease manifestations in various patients. We believe that a mechanistic approach to OSA therapy is viable such that selected patients could undergo pharmacological manipulations to treat the factor underlying disease in a particular afflicted individual. Further efforts into defining disease pathogenesis should allow new therapeutic targets in OSA to emerge.

### REFERENCES


Future of sleep apnea therapy using a mechanistic approach