OBSTRUCTIVE SLEEP APNEA is a disorder caused by recurrent episodes of upper airway obstruction during sleep. These episodes lead to repeated oxyhemoglobin desaturations and arousals from sleep, accounting for significant neurocognitive, metabolic, and cardiovascular morbidity and mortality. Obesity, male sex, age, and postmenopausal status are major risk factors for this disorder. Changes in adiposity and body fat distribution may mediate effects of these risk factors on sleep apnea susceptibility. Nevertheless, the impact of these factors on upper airway function during sleep is not well understood. In this minireview, we outline a conceptual approach to characterizing upper airway function and consider the impact of adiposity and body fat distribution on pharyngeal neuromuscular control. Upper airway structural alterations in obesity are related to adipose deposition around the pharynx, which can increase its collapsibility or critical pressure \( (P_{\text{crit}}) \). In addition, obesity and, particularly, central adiposity lead to reductions in resting lung volume, resulting in loss of caudal traction on upper airway structures and parallel increases in pharyngeal collapsibility. Metabolic and humoral factors that promote central adiposity may contribute to these alterations in upper airway mechanical function and increase sleep apnea susceptibility. In contrast, neural responses to upper airway obstruction can mitigate these mechanical loads and restore pharyngeal patency during sleep. Current evidence suggests that these responses can improve with weight loss. Improvements in these neural responses with weight loss may be related to a decline in systemic and local pharyngeal concentrations of specific inflammatory mediators with somnogenic effects.

Obstructive sleep apnea; upper airway obstruction; neuromuscular control; pharyngeal neuromechanical function

MODELING UPPER AIRWAY FUNCTION DURING SLEEP

Investigators have demonstrated that the upper airway can be modeled as a simple collapsible conduit or Starling resistor (25). In this model, a collapsible segment is subject to a surrounding or critical pressure \( (P_{\text{crit}}) \) that governs its collapsibility. \( P_{\text{crit}} \) determines the degree of upper airway obstruction as follows. First, the upper airway collapses and flow limits on inspiration as the downstream (tracheal) pressure falls below \( P_{\text{crit}} \). As downstream pressure falls, inspiratory airflow rises to a maximal level and plateaus thereafter, becoming independent of further decreases in downstream pressure. This pattern is often associated with inspiratory snoring, which is due to repeated collapse and reopening of the upper airway as flow oscillates around a maximal level. Nonetheless, the flow-limited upper airway does not occlude, indicating that downstream “suction” pressures cannot account for the development of complete obstruction in sleep apnea patients.

To occlude the upper airway, the pressure upstream to the collapsible (flow-limiting) site must become lower than \( P_{\text{crit}} \). This concept has been demonstrated experimentally in normal individuals. When upstream pressure is lowered to subatmospheric levels, the upper airway occludes and recurrent obstructive apneas ensue (44). In contrast, when \( P_{\text{crit}} \) rises above atmospheric pressure, as it does in patients with sleep apnea, recurrent obstructive apneas are observed. Methods for manipulating nasal pressure during sleep have been used to demonstrate quantitative differences in \( P_{\text{crit}} \) that distinguish groups with varying degrees of upper airway obstruction clinically from health (normal breathing) to disease (obstructive sleep apnea) (24, 69, 81–83, 94). Therapeutic maneuvers that mitigate sleep apnea are generally characterized by a reduction in upper airway collapsibility during sleep (8, 25, 33–36, 59, 63, 81, 82), suggesting that changes in pharyngeal collapsibility mediate therapy and pathogenic effects on sleep apnea susceptibility (Fig. 1).
Elevations in pharyngeal collapsibility ($P_{crit}$) in sleep apnea patients could be related to anatomic alterations and/or disturbances in its neuromuscular control. Physiological methods have been recently developed to characterize pharyngeal structural and neuromuscular control in sleeping individuals (68). These methods involve extinguishing pharyngeal neuromuscular activity initially by raising nasal pressure and then lowering pressure abruptly to induce upper airway obstruction. The nasal pressure at which the airway first occludes (when neuromuscular activity remains low) provides a measure of the passive $P_{crit}$ and reflects the impact of anatomic factors on pharyngeal collapsibility. Thereafter, time-dependent increases in neuromuscular activity occur in response to the airflow obstruction. This activity is elicited by chemical and mechanical afferents that can mitigate the obstruction and restore upper airway patency (10, 50, 84, 85, 100, 101). Subsequent increases in airflow lead to an overall decrease in the nasal pressure at which the airway occludes in the activated (active $P_{crit}$) compared with the passive condition (51, 56, 63–65, 69, 80, 84).

Investigators have applied these methods to determine the role played by structural and neuromuscular defects in the pathogenesis of obstructive sleep apnea (56, 69). Recent studies have documented a structural/anatomic predisposition to upper airway obstruction in apneic patients compared with normal individuals, as characterized by elevations in passive $P_{crit}$ and reflects the impact of anatomic factors on pharyngeal collapsibility. Thereafter, time-dependent increases in neuromuscular activity occur in response to the airflow obstruction. This activity is elicited by chemical and mechanical afferents that can mitigate the obstruction and restore upper airway patency (10, 50, 84, 85, 100, 101). Subsequent increases in airflow lead to an overall decrease in the nasal pressure at which the airway occludes in the activated (active $P_{crit}$) compared with the passive condition (51, 56, 63–65, 69, 80, 84).

In studies, investigators demonstrated that obesity, a major risk factor for sleep apnea, leads to elevations in passive $P_{crit}$, reflecting increased mechanical (anatomic) loading of pharyngeal structures. Early studies in isolated animal upper airway preparations suggested that obesity might exert its mechanical effects by increasing soft tissue loads on the pharynx (46). When external loads were applied to the anterior neck and submandibular area, $P_{crit}$ rose substantially as pressures within the bony mandibular enclosure rose around the collapsible pharyngeal segment. Subsequently, investigators demonstrated that the passive $P_{crit}$ is also influenced by anterior traction on pharyngeal surrounding structures such as the tongue and mandible (40), which can decrease the passive $P_{crit}$ (75). In human studies, investigators further demonstrated that mandibular advancement can enlarge the bony enclosure and lower $P_{crit}$ (5, 6, 31) in lean, but not obese, subjects (37, 60). The failure to decrease passive $P_{crit}$ with mandibular advancement in obese subjects may be related to adipose deposition in peripharyngeal fat pads, which may cause collapse of lateral, rather than anterior, pharyngeal structures (78, 79). These fatty deposits are particularly pronounced in men with central adiposity compared with women with peripheral adiposity. Thus obesity and central adiposity can crowd the pharyngeal lumen and increase surrounding tissue pressures, leading to elevations in pharyngeal collapsibility when neuromuscular activity wanes during sleep.

Alternatively, obesity and, especially, central obesity can increase upper airway collapsibility through mechanical effects on lung volume. As fat accumulates around the torso, functional residual capacity falls (92), leading to a loss of caudal traction on upper airway structures from mediastinal, rib cage, and cervical strap muscle attachments (39, 98, 99). As caudal traction decreases, pharyngeal collapsibility can increase substantially (75, 88–90, 97–99), owing to a decrease in axial tension within the pharyngeal airway wall (75). A decrease in axial tension also attenuates responses to anterior displacement in humans (37) and experimental animals (75, 76). Recently, investigators provided evidence that the passive $P_{crit}$ is in-

**OBESITY AND UPPER AIRWAY MECHANICAL FUNCTION**

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versely related to the end-expiratory lung volume in humans, such that airway collapsibility increases when lung volume falls (95). An increase in the passive $P_{\text{crit}}$ could also account for the observation that the minimally effective therapeutic continuous positive airway pressure decreases (26) and sleep apnea severity improves when end-expiratory lung volume is increased experimentally (12, 27). Thus reductions in lung volume can also account for increases in pharyngeal collapsibility in obesity.

The passive $P_{\text{crit}}$ has been quantified in human cohorts to measure the effects of obesity and fat distribution on upper airway mechanical function (38, 45). Obesity has been associated with significant elevations in passive $P_{\text{crit}}$ of 1.40 (1.01–1.78) cmH$_2$O per 10 kg/m$^2$ elevation in body mass index (BMI) across a broad range of BMIs. In addition to obesity, sex-related differences have been observed to elevate the passive $P_{\text{crit}}$ by $\sim$2 cmH$_2$O in men compared with women, who were matched for the degree of obesity (BMI), sleep apnea severity (respiratory disturbance index), and age (45). These differences in passive $P_{\text{crit}}$ may be largely related to differences in the distribution of adiposity, rather than sex-related differences in upper airway anatomy per se, since elevations in passive $P_{\text{crit}}$ per unit increase in BMI were greater in men than in women. Specifically, a 0.78-cmH$_2$O greater increase in passive $P_{\text{crit}}$ was observed in men than in women: 1.67 vs. 0.95 cmH$_2$O per 10 kg/m$^2$. These findings suggest that obesity and, particularly, central adiposity impose mechanical loads on the upper airway, which can increase sleep apnea susceptibility substantially. Nevertheless, it is not known whether pathogenic changes in passive $P_{\text{crit}}$ are primarily due to fat accumulation around the torso or in tissues surrounding the pharynx.

Metabolic and humoral factors that determine the distribution of adiposity may ultimately be responsible for elevations in pharyngeal collapsibility. Central adiposity increases with age and, particularly, as women pass through menopause. Leptin, a recognized satiety factor produced by adipose tissue, regulates body composition and the distribution of adiposity (11). Leptin is produced in abundance by subcutaneous adipose tissue, particularly in women, and limits central adiposity. In recent experiments, we and others have begun to distinguish effects of obesity and leptin on upper airway collapsibility in mice (58). Pressures were manipulated at the nose in anesthetized wild-type and leptin-deficient lean and obese mice to determine the passive $P_{\text{crit}}$ (51). In pilot experiments, we found evidence to suggest that obesity and leptin deficiency are associated with marked elevations in passive $P_{\text{crit}}$, potentially implicating these factors in the pathogenesis of upper airway obstruction during sleep. Increases in obesity and adiposity (fat content) may also account for the high prevalence of glucose intolerance (57, 62) and frank diabetes mellitus (22) in patients with obstructive sleep apnea. Thus humoral factors leading to visceral fat deposition will increase pharyngeal mechanical loads and increase sleep apnea susceptibility.

**OBESITY AND UPPER AIRWAY NEURAL CONTROL**

Current evidence suggests that obesity may also impact upper airway neural control. Its impact can be estimated from prior cross-sectional and longitudinal (weight loss) studies. We previously demonstrated that weight loss leads to an $\sim$6.2-cmH$_2$O fall in $P_{\text{crit}}$ per 10 kg/m$^2$ decrease in BMI in apneic men (81), which may have been due to reductions in the passive and/or active $P_{\text{crit}}$. A similar decrease in BMI has been associated with an $\sim$1.7-cmH$_2$O decrease in passive $P_{\text{crit}}$ (see above). The remaining 4.5-cmH$_2$O decrease is attributable to reductions in the active $P_{\text{crit}}$, suggesting a concomitant recovery in active neuromuscular control with weight loss. In pilot studies, similar improvements in active $P_{\text{crit}}$ have been observed in apneic women undergoing massive weight loss after bariatric surgery.

What might account for an overall decrease in compensatory neuromuscular control mechanisms in obesity? Obesity and, particularly, visceral adiposity have been associated with defects in upper airway neuromuscular control and increases in sleep apnea susceptibility and severity (104). These effects may be related to increased circulating levels of inflammatory cytokines (3, 4, 7, 14, 17, 23, 30, 41, 54, 72, 86, 106). These cytokines include TNF-α, TNF-α receptor I, IL-6, and IL-1β, which have somnogenic central nervous system activity (18, 19, 47–49, 66, 96, 104). In particular, TNF-α stimulates the membrane expression and release of its soluble receptor TNF-α receptor I, which rises in sleep-deprived subjects (93), and mediates the somnogenic effect of TNF-α centrally (16, 18, 48, 96). As obesity progresses and sleep apnea develops, nocturnal disturbances in sleep and gas exchange can trigger further elevations in inflammatory cytokines (1, 3, 15, 20, 32, 42, 54, 55, 67, 70, 71, 74, 77, 91, 102, 107), further aggravating pharyngeal neuromuscular dysfunction (15, 20, 54, 55, 67, 70, 71, 74). Factors that decrease circulating levels of inflammatory cytokines, including continuous positive airway pressure and etanercept (3, 103, 104), may help improve sleep apnea by decreasing upper airway collapsibility during sleep (8, 25, 33–36, 59, 63, 81, 82). It is therefore possible that humoral effects of obesity and visceral adiposity play a role in the pathogenesis and progression of sleep apnea by blunting compensatory upper airway neuromuscular responses.

Sleep apnea has also been associated with inflammation of upper airway structures. Investigators have demonstrated in a rodent model that repeated collapse of the pharynx can increase the expression of several inflammatory genes, including macrophage inflammatory protein-2, TNF-α, IL-1β, and P-selectin (2, 73). These cytokines can trigger an inflammatory cascade in periluminal pharyngeal tissues, leading to immune cell infiltration and remodeling of extracellular matrix tissue (87). The resulting ultrastructural changes in pharyngeal tissues have been associated with neurosensory deficits to pinprick two-point discrimination (9, 43, 61, 87). Sensory deficits may impair protective reflex responses to negative intraluminal pressures and compromise compensatory neuromuscular responses to airway obstruction during sleep (13, 28, 29, 52, 53, 105). Thus local, as well as systemic, inflammatory responses may contribute to disturbances in upper airway neuromuscular control and increase sleep apnea susceptibility in obese patients.

**CONCLUSIONS**

In summary, obstructive sleep apnea is caused by elevations in upper airway collapsibility during sleep, which are produced by alterations in upper airway anatomy and disturbances in neuromuscular control. Current evidence suggests that obesity...
and central adiposity lead to alterations in pharyngeal neural and mechanical control that increase collapsibility and sleep apnea susceptibility. Female sex and leptin activity may mitigate structural loads on the pharynx in obese individuals, since they are associated with a preservation of upper airway neuromuscular responses. In contrast, systemic and local (pharyngeal) inflammatory mechanisms may compromise neuromuscular control mechanisms in obesity. These mechanisms may further aggravate underlying defects in upper airway neuromechanical control and lead to a worsening of sleep apnea over time. Complementary approaches to the study of upper airway function in humans and animals will help establish specific pathogenic mechanisms and probe specific humoral and genetic factors that modulate the development and expression of this disorder.

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DISCLOSURES

No conflicts of interest are declared by the author(s).

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