ORIGINAL ARTICLE

Enhanced Upper-Airway Muscle Responsiveness Is a Distinct Feature of Overweight/Obese Individuals without Sleep Apnea

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Abstract

Rationale: Body habitus is a major determinant of obstructive sleep apnea (OSA). However, many individuals do not have OSA despite being overweight/obese (body mass index > 25 kg/m^2) for reasons that are not fully elucidated.

Objectives: To determine the key physiologic traits (upper-airway anatomy/collapsibility, upper-airway muscle responsiveness, chemoreflex control of ventilation, arousability from sleep) responsible for the absence of OSA in overweight/obese individuals.

Methods: We compared key physiologic traits in 18 overweight/obese subjects without apnea (apnea–hypopnea index < 15 events per hour) with 25 overweight/obese matched patients with OSA (apnea–hypopnea index ≥ 15 events per hour) and 11 normal-weight nonapneic control subjects. Traits were measured by repeatedly lowering continuous positive airway pressure to subtherapeutic levels for 3 minutes during non-REM sleep.

Measurements and Main Results: Overweight/obese subjects without apnea exhibited a less collapsible airway than overweight/obese patients with apnea (critical closing pressure: -3.7 ± 1.9 vs. 0.6 ± 1.2 cm H$_2$O; $P = 0.003$; mean $\pm$ 95% confidence interval),

but a more collapsible airway relative to normal-weight control subjects (-8.8 ± 3.1 cm H$_2$O; $P < 0.001$). Notably, overweight/obese subjects without apnea exhibited a threefold greater upper-airway muscle responsiveness than both overweight/obese patients with apnea (Δgenioglossus EMG/Δepiglottic pressure: -0.49 [-0.22 to -0.79] vs. -0.15 [-0.09 to -0.22] %max/cm H$_2$O; $P = 0.008$; mean [95% confidence interval]) and normal-weight control subjects (-0.16 [-0.04 to -0.30] %max/cm H$_2$O; $P = 0.02$). Loop gain was elevated (more negative) in both overweight/obese groups and normal-weight control subjects ($P = 0.02$). Model-based analysis demonstrated that overweight/obese individuals without apnea rely on both more favorable anatomy and collapsibility and enhanced upper-airway dilator muscle responses to avoid OSA.

Conclusions: Overweight/obese individuals without apnea have a moderately compromised upper-airway structure that is mitigated by highly responsive upper-airway dilator muscles to avoid OSA. Elucidating the mechanisms underlying enhanced muscle responses in this population may provide clues for novel OSA interventions.

Keywords: apnea phenotypes; upper airway muscles; obesity; control of breathing; mathematical model

At a Glance Commentary

Scientific Knowledge on the Subject: Obesity is a major risk factor for obstructive sleep apnea (OSA). However, many individuals who are overweight/obese do not develop OSA for reasons that are not fully understood.

What This Study Adds to the Field: Overweight/obese individuals without apnea exhibit markedly enhanced upper-airway muscle responsiveness compared with overweight/obese patients with OSA, and also compared with normal-weight nonapneic control subjects. These characteristics tend to mitigate OSA by counteracting a moderate anatomical compromise. Quantitatively, the more favorable anatomy and enhanced muscle responsiveness in overweight/obese individuals without apnea are both essential for protecting against the development of OSA.

Obstructive sleep apnea (OSA) is a prevalent disease with major cardiovascular and neurocognitive consequences. Obesity is a major risk factor for OSA, and most individuals manifest OSA with sufficient additional body weight (1). However, many overweight/obese individuals do not have OSA for reasons that remain unclear.

Mechanistically, OSA is caused primarily by a narrow, collapsible upper airway (2, 3). Because of increased fat deposition, overweight/obese individuals generally have a more collapsible airway than normal-weight individuals (4–8), yet the modest relationship between body mass index (BMI) and upper-airway collapsibility (3, 9) indicates that some individuals gain weight without major upper-airway compromise.

Whether a collapsible airway ultimately yields OSA also depends on additional nonanatomic physiologic traits (2, 4, 10–17). In individuals with a highly collapsible airway, enhanced upper-airway dilator muscle responsiveness during sleep is theoretically necessary to provide a level of ventilation that is compatible with stable breathing and sleep. Indeed, evidence indicates that overweight/obese individuals without apnea have a greater capacity to activate upper-airway muscles and increase airflow during sleep compared with BMI-matched patients with OSA (4, 14). However, other nonanatomic traits, such as a higher (less-sensitive) arousal threshold or a reduced ventilatory drive response to asphyxia (lower loop gain), can also protect against OSA (11, 18, 19).

Accordingly, we sought to determine which key physiologic traits protect overweight/obese individuals from developing OSA. We tested the primary hypotheses that overweight/obese individuals without apnea not only have a less collapsible upper airway (lower critical closing pressure [Pcrit]), but also have more responsive pharyngeal muscles (greater genioglossus EMG [EMGgg] response to negative pressure) than patients with OSA. We studied 11 new participants and combined their data with our larger phenotype study (2). In total, OSA traits were examined in 18 overweight/obese (BMI > 25 kg/m^2) nonapneic control subjects (apnea–hypopnea index [AHI] < 15 events per hour) and compared with 25 overweight/obese patients with OSA (AHI > 15) and 11 normal-weight (BMI < 25 kg/m^2) control subjects.

Methods

Subjects

All overweight/obese nonapneic control subjects aged 25–70 years from our larger study (2) were included. Patients with OSA were selected to match this group for BMI, age, and sex. All normal-weight nonapneic control subjects were included for comparison. The 11 new participants were studied to better match the groups for sex and enhance statistical power. For details, see the online supplement.

Polysomnography and Physiologic Traits

Details have been described previously (2, 16). Briefly, participants presented for three overnight sleep studies. First, routine polysomnography determined the presence or absence of OSA. Hypopneic events (>10 s) were scored as those that caused a 3% oxygen desaturation or arousal from sleep (20). Subsequently, over 2 nights we measured key physiologic traits by repeatedly lowering continuous positive airway pressure (CPAP) below therapeutic levels to challenge the pharyngeal airway; drops were performed for 3-minute

Table 1. Patient Characteristics

Characteristics	Overweight/Obese Subjects without Apnea (n = 18)	Overweight/Obese Patients with OSA (n = 25)	Normal-Weight Control Subjects without Apnea (n = 11)
Male:female*	9:9	16:9	6:5
Age, yr	44 ± 5	48 ± 4	41 ± 8
Body mass index, kg · m^{-2}	31 ± 2	32 ± 1	22 ± 1†
AHI total, h^{-1}	8.0 ± 2.1	41.5 ± 8.8‡	4.6 ± 3.0
AHI supine non-REM, h^{-1}	6.3 ± 2.4	42.0 ± 9.4‡	3.7 ± 3.0
AHI supine REM, h^{-1}	20.0 ± 6.5	43.9 ± 8.5‡	10.5 ± 5.9

Definition of abbreviations: AHI = apnea–hypopnea index; OSA = obstructive sleep apnea.
Values are mean ± 95% confidence interval.
Body mass index is the weight divided by the squared height.
AHI during REM was available in 14 of 18, 21 of 25, and 8 of 11 participants, respectively.
*Fisher exact test, not significant (P = 0.6). One-way analysis of variance with Student-Newman-Keuls *post hoc* analysis was used for continuous variables.
†P < 0.001 normal-weight versus both overweight/obese groups.
‡P < 0.001 overweight/obese patients with OSA versus both nonapneic groups.

intervals during supine non-REM sleep. We measured ventilation and CPAP level by a nasal mask, epiglottic pressure (Pepi), and EMGgg using fine-wire electrodes. Traits were measured as follows (*see* Figure E1 in the online supplement) (2, 16, 17):

1. Airway collapsibility: the critical CPAP level Pcrit yielding zero airflow through a passive airway (x-intercept of a linear regression between peak-inspiratory flow vs. mask pressure on the third to fifth breaths following the CPAP drop, if breaths were flow limited).
2. Upper-airway muscle responsiveness: the increase in peak EMGgg (%maximum) per change in nadir Pepi across each CPAP drop.
3. Loop gain: the increase in ventilatory drive (measured as the ventilatory overshoot following a switch to optimal CPAP) in response to a steady-state reduction in ventilation.
4. Arousal threshold: the nadir Pepi on the breath preceding arousal from sleep.

Model-based Analysis

To examine how the traits manifest the absence of OSA in overweight/obese individuals without apnea, we combined the traits using a mathematical model that graphically illustrates their contribution to OSA (16, 17) (*see* Figure E2). For this purpose we remeasured the traits in units of ventilation as follows (16):

1. Anatomy/collapsibility: the ventilation "Vpassive" through a passive airway (CPAP = 0 cm H_2O) at eupneic ventilatory drive (y-intercept of a plot of ventilation vs. CPAP).
2. Upper-airway muscle effectiveness ("upper-airway gain"): the compensatory increase in ventilation across the drop (the activated level at the end of the drop minus the "passive" ventilation at the start) per increase in ventilatory drive (measured as the ventilatory overshoot following a switch to optimal CPAP).
3. Arousal threshold: the ventilatory drive preceding arousal.

The traits were subsequently combined to calculate two intermediate physiologic parameters: "Vactive" is the ventilation that can be achieved through a maximally active airway without arousal, and "Varousal" is the minimum ventilation that can be tolerated without arousal. The difference between Varousal and Vactive, called the physiologic "gap," predicts whether stable breathing is possible or patients will exhibit OSA (17). A positive "gap" quantifies the degree of ventilatory insufficiency and predicts the presence of OSA (the ventilation needed to avoid arousal cannot be achieved through the activated airway; Vactive < Varousal). A negative "gap" quantifies the degree of ventilatory reserve and predicts that stable breathing is possible without arousal (Vactive > Varousal).

Statistical Analysis

One-way analysis of variance (ANOVA) assessed trait differences between groups. As necessary, transforms were applied before
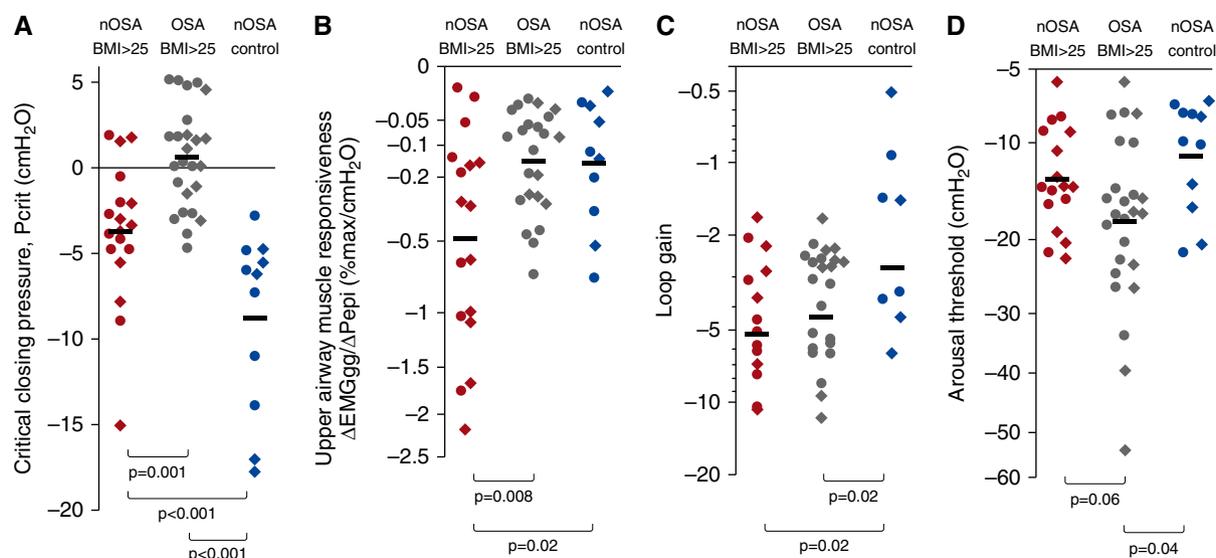

Figure 1. Physiologic differences between overweight/obese nonapneic individuals (nOSA BMI > 25), overweight/obese patients with OSA (OSA BMI > 25), and normal-weight control subjects (nOSA control). (*A*) The upper airway is less collapsible (Pcrit is lower) in overweight/obese nOSA versus overweight/obese OSA, but is more collapsible than normal-weight control subjects. (*B*) Upper-airway dilator muscles are markedly more responsive in overweight/obese nOSA compared with both overweight/obese OSA and normal-weight control subjects. Responsiveness is defined as the genioglossus electromyogram (EMGgg) response to negative epiglottic pressure, ΔEMGgg/ΔPepi (EMGgg is reported relative to maximum achievable activity). (*C*) Loop gain is elevated (more negative) in both overweight/obese groups versus nOSA control subjects. (*D*) Overweight/obese nOSA individuals exhibit a similar arousal threshold to nOSA control subjects. The arousal threshold is elevated (more negative) in OSA versus nOSA control subjects. Men and women are denoted by *circles* and *diamonds*, respectively. Mean data are illustrated by *horizontal bars*. Data in *B* and *D* were square-root transformed before statistical analysis to achieve normally distributed data; these data are plotted on a square-root scale. Data in *C* were log-transformed before statistical analysis; these data are plotted on a logarithmic scale. One-way analysis of variance with Student-Newman-Keuls *post hoc* analysis were used to compare groups. Measures of upper-airway responsiveness could be made in 17 of 18 (nOSA BMI > 25), 23 of 25 (OSA BMI > 25), and 10 of 11 (nOSA control) individuals. Measures of loop gain could be made in 14 of 18 (nOSA BMI > 25), 23 of 25 (OSA BMI > 25), and 8 of 11 (nOSA control) individuals. BMI = body mass index; OSA = obstructive sleep apnea; Pcrit = critical closing pressure.

statistical analysis to provide normally distributed data (square root transform for upper-airway muscle responsiveness [EMGgg/Pepi] and arousal threshold [Pepi], and log10 transform for loop gain); reported means and 95% confidence intervals reflect back-transformed values. Two-way ANOVA assessed trait differences between groups adjusting for sex. Multiple logistic regression examined whether enhanced muscle responsiveness and effectiveness contributed to the absence of OSA in addition to upper-airway collapsibility (Pcrit). P less than 0.05 was considered statistically significant.

Results

Subject characteristics are detailed in Table 1. Despite similar BMI, overweight/obese subjects without apnea have a less-collapsible airway (lower Pcrit) compared with overweight/obese patients with apnea (Figure 1A). However, the upper-airway anatomy/collapsibility of overweight/obese subjects without apnea remained moderately compromised (higher Pcrit) versus normal-weight control subjects. Overweight/obese subjects without apnea exhibited approximately threefold greater upper-airway muscle responsiveness versus patients with OSA and normal-weight control subjects (Figure 1B). Loop gain was similar between overweight/obese subjects without apnea and patients with OSA; both groups exhibited elevated loop gain versus normal-weight control subjects (Figure 1C). Arousal thresholds were elevated in patients with OSA versus normal-weight control subjects (Figure 1D). After adjusting for potential sex effects (two-way ANOVA), the aforementioned group differences remained significant for all traits; there were no significant effects of sex or significant interactions between sex and group.

Measurement of the traits for model-based analysis revealed similar results. The upper-airway muscle effectiveness (upper-airway gain) was threefold greater in overweight/obese subjects without apnea compared with patients with apnea (Figure 2). Vpassive was significantly reduced in overweight/obese OSA versus normal-weight control subjects (34 ± 17% vs. 78 ± 9%; $P < 0.01$; mean ± 95% confidence interval); Vpassive in overweight/obese subjects without apnea

(56 ± 18%) was midway between overweight/obese OSA and normal-weight control subjects. The ventilatory drive at arousal was similar between groups.

Model-based analyses are illustrated in Figures 3A–3C. Because of the enhanced muscle responses and moderately compromised anatomy, the overweight/obese subjects without apnea exhibited a small negative "gap" (−11% of eupneic ventilation; calculated from group summary data) consistent with the absence of OSA. By contrast, the overweight/obese patients with apnea exhibited a large positive "gap" (+38% of eupneic ventilation) consistent with OSA. As expected, the normal-weight nonapneic control subjects had a large negative gap (−21% of eupneic ventilation) consistent with a large reserve against OSA (see Figure 3D for individual data). We calculated that if the overweight/obese subjects without apnea had the same upper-airway responsiveness and effectiveness or the same upper-airway collapsibility (Vpassive) as the group with apnea, they would have a positive gap (+16% or +11% of eupneic ventilation) and would exhibit OSA (Figure 4).

Further analysis (multiple logistic regression) illustrates that upper-airway muscle responsiveness (Figure 5A) and effectiveness (Figure 5B) help to explain the presence of OSA beyond upper-airway collapsibility alone. Individuals with greater upper-airway collapsibility require a greater upper-airway muscle responsiveness and effectiveness to avoid OSA.

Discussion

The major finding of the current study is that enhanced muscle responsiveness is a distinct feature of overweight/obese individuals without moderate-severe OSA. Overweight/obese individuals without apnea exhibit approximately three times greater pharyngeal muscle responsiveness during sleep compared with their OSA counterparts and normal-weight control subjects. Our study also confirmed that overweight/obese individuals without apnea have an upper-airway structural advantage (lower Pcrit) relative to overweight/obese patients with OSA (4–8); we extend these findings to demonstrate that the collapsibility of overweight/obese individuals without apnea is considerably compromised (higher Pcrit) when considered alongside normal-weight
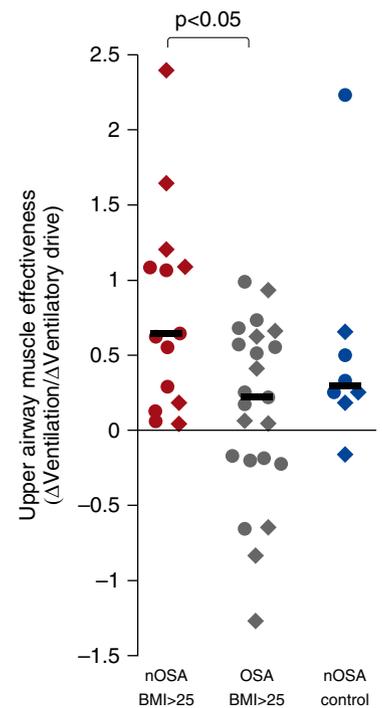

Figure 2. Upper-airway muscle effectiveness (upper-airway gain) is threefold greater in overweight/obese individuals without apnea (nOSA BMI > 25) versus overweight/obese patients with OSA (OSA BMI > 25). Data from normal-weight control subjects (nOSA control) are shown for comparison. Median data are illustrated by *horizontal bars*. Men and women are denoted by *circles* and *diamonds*, respectively. Measures of upper-airway muscle effectiveness could be made in only 14 of 18 (nOSA BMI > 25), 23 of 25 (OSA BMI > 25), and 8 of 11 (nOSA control) individuals because of difficulties measuring loop gain. Groups were compared using one-way analysis of variance on ranks with Dunn *post hoc* analysis. BMI = body mass index; OSA = obstructive sleep apnea.

control subjects. Indeed, the mean Pcrit of −3.7 cm H_2O in overweight/obese subjects without apnea was within the vulnerable range for moderate-severe OSA (−5 cm H_2O or above) (2, 9). Overall, our data show that overweight/obese individuals without apnea escape OSA via highly effective upper-airway muscle responses that compensate for a moderately compromised anatomy.

Novel Physiologic Insights
Examination of our model-based analysis demonstrates that overweight/obese individuals without apnea are reliant on their enhanced muscle responsiveness to avoid OSA. We note that overweight/obese individuals without apnea have a minimal
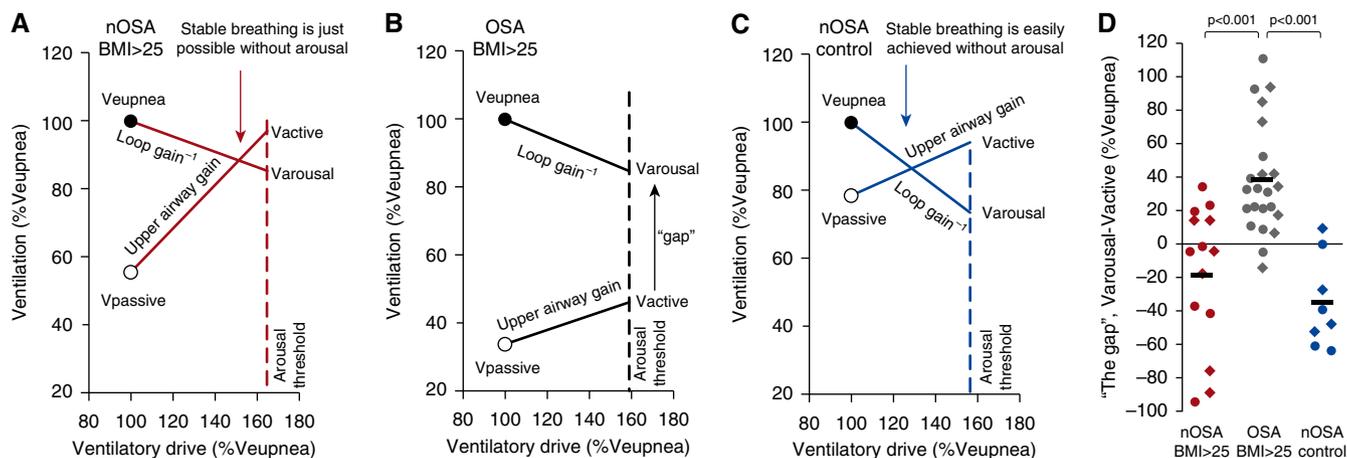
Figure 3. Combining the four physiologic traits graphically using a mathematical model illustrates how they interact to manifest the absence or presence of obstructive sleep apnea (OSA). (*A–C*) Group data are shown for each trait measured in units of ventilation. Veupnea is the ventilation on optimal continuous positive airway pressure. Vpassive is the functional anatomy/collapsibility represented as the ventilation off continuous positive airway pressure at normal ventilatory drive. The *upper-airway gain line* describes the functional compensatory increase in ventilation with increased ventilatory drive (which activates upper-airway muscles); this line indicates the achievable ventilation. The *loop gain line* illustrates the level of ventilatory drive that will eventually develop for any reduction in ventilation (e.g., because of rising carbon dioxide). If these diagonal lines intersect at a level of ventilatory drive below the arousal threshold (*vertical dashed line*) then stable breathing is possible during sleep; otherwise, OSA should occur. (*A*) On average, the physiologic traits of overweight/obese subjects without apnea (nOSA) are consistent with stable breathing: Note that the upper airway is so effective (steep slope of *upper-airway gain line*) that stable breathing occurs (intersection of *diagonal lines* before the arousal threshold), despite a moderately compromised anatomy. The maximum ventilation achievable without arousal (Vactive) marginally exceeds the minimum level of ventilation that can be tolerated without arousal (Varousal). (*B*) The traits of overweight/obese patients with apnea are consistent with OSA. Stable breathing is not possible because the achievable ventilation (Vactive) is below the level needed to prevent arousal (Varousal). (*C*) The traits of healthy normal-weight control subjects are consistent with stable breathing. The favorable anatomy provides for stable breathing regardless of their modest upper-airway responsiveness (the slope is no steeper than in OSA). (*D*) Ultimately, the "gap" (Varousal − Vactive) predicts whether OSA will occur (mean data are illustrated by *horizontal bars*). In OSA, the "gap" is positive and significantly greater than in overweight/obese subjects without apnea (analysis of variance), in whom the gap is negative. Men and women are denoted by *circles* and *diamonds*, respectively. Of note, measures of the "gap" could be made in 14 of 18 (nOSA BMI > 25), 23 of 25 (OSA BMI > 25), and 8 of 11 (nOSA control) individuals because of difficulties measuring loop gain. Vactive = Vpassive + (upper-airway gain) × (arousal threshold − 100). Varousal = 100 − (loop gain)$^{-1}$ × (arousal threshold − 100). BMI = body mass index.

reserve (the "gap" is approximately 10% of eupneic ventilation) to protect against the development of OSA, such that any added deficiency would cause OSA. Using the model, we showed that if overweight/obese individuals without apnea are given the same upper-airway responsiveness or collapsibility as the group with apnea, they would exhibit OSA (Figure 4). Consistent with this view, in REM sleep, when muscle activity becomes more severely compromised (15, 21), the otherwise nonapneic group exhibited OSA of moderate severity (Table 1). By contrast, the groups with minimal muscle responsiveness did not exhibit an increased AHI in REM. These findings taken together provide conclusive, quantitative evidence of the essential role of upper-airway muscle responsiveness for the prevention of OSA in those with a vulnerable anatomy.

Based on the near-identical muscle responsiveness of overweight/obese patients with OSA and normal-weight control subjects (Figure 1B), our study demonstrates that impaired genioglossus

muscle responsiveness is probably not a primary cause of OSA in overweight/obese individuals *per se*. Rather, the reduced upper-airway compensatory responses in this population only seem to be reduced in previous work (4), because responsiveness has been compared with weight-matched subjects without apnea, who this study shows have a "supranormal" responsiveness. Thus, we interpret that OSA occurs with obesity primarily because of its effect on upper-airway structure/collapsibility (and elevated loop gain, noting the difference in Figure 1C). However, enhanced upper-airway muscle responsiveness, when present, acts as a key effect modifier that is capable of averting OSA in many individuals.

Our data confirm previous work illustrating that individuals without apnea can achieve greater upper-airway dilator muscle activation during sleep (increased EMGgg and ventilation above passive conditions) versus BMI-matched patients

with OSA (4, 14). We emphasize, however, that the increase in EMGgg and ventilation during sleep reflects two key traits: the upper-airway responsiveness and the arousal threshold (i.e., Vactive − Vpassive = [upper-airway gain] × [arousal threshold − 100]). A novel finding of our study is that, among the overweight/obese population, individuals without apnea exhibit an enhanced upper-airway responsiveness *per se* (change in EMGgg per unit change in Pepi), whereas the arousal threshold is similar between groups.

Our data also suggest that loop gain is increased in overweight/obese individuals (vs. normal-weight control subjects) regardless of whether or not such individuals have OSA. An increase in loop gain may be an important additional mechanism by which individuals who gain weight become predisposed to OSA. A possible mechanism is the increased circulating leptin in overweight individuals, which is known to raise chemosensitivity (22).
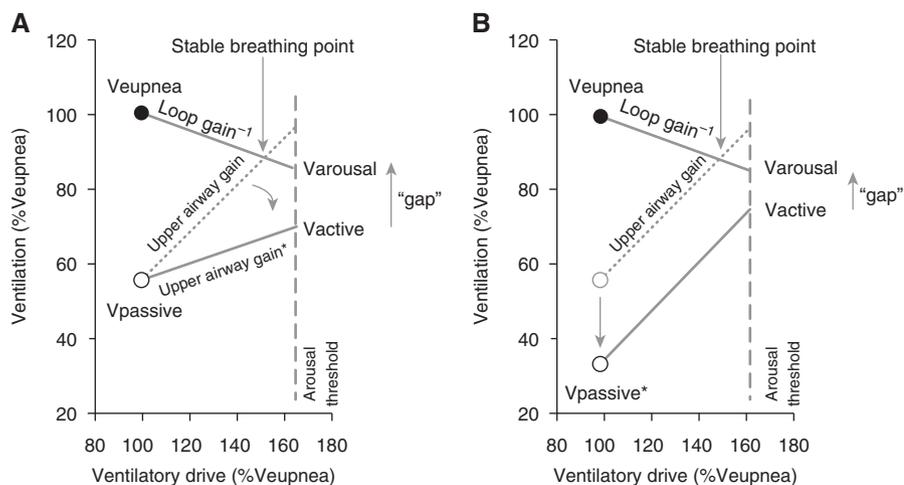
Figure 4. Essential roles of the greater upper-airway muscle responsiveness and reduced upper-airway collapsibility in overweight/obese subjects without apnea versus patients with apnea. The physiologic traits of subjects without apnea are combined mathematically (Figure 3A) to illustrate why stable breathing is possible without arousal from sleep in overweight/obese individuals without obstructive sleep apnea (OSA); note that the intersection of the *loop gain line* and *upper-airway gain line* (stable breathing point) lies to the left of the arousal threshold (*dashed vertical line*). (*A*) If overweight/obese subjects without apnea had the upper-airway effectiveness (or "gain") of the OSA group (*upper-airway gain; *solid line*) then the maximum achievable ventilation during non-REM sleep (Vactive) would instead be below the minimum tolerable ventilation (Varousal), providing a physiologic "gap" (+16% of Veupnea) that cannot be overcome without arousal. Hence, the effective upper-airway muscle response in subjects without apnea can be considered essential for the observed absence of OSA. (*B*) A similar result is observed for the anatomy/collapsibility. If Vpassive is reduced to the level of the OSA group (by 22% of eupneic ventilation; difference in mean values), the gap would be become positive (+11% of Veupnea) such that OSA would occur. Thus the less-vulnerable anatomy (higher Vpassive) in overweight/obese subjects without apnea is also essential for their avoidance of OSA.

Mechanisms of Advantageous Physiology in Overweight and Obese Individuals without Apnea

The mechanisms of less-pronounced upper-airway collapsibility in overweight/obese subjects without apnea versus weight-matched patients with apnea are currently being elucidated. Compared with patients with OSA, weight-matched individuals without apnea tend to have reduced fat distribution to the neck (23), and at a local pharyngeal level exhibit reduced tongue fat (8) and parapharyngeal fat pad volumes (5–8, 24, 25). Overweight/obese individuals without apnea also have craniofacial features that provide a greater anatomic reserve for fat deposition by increased intramandibular volume (7, 26, 27). These advantageous structural differences are likely under genetic control given the familial nature of upper-airway structure and OSA (28–31).

The origin of enhanced muscle responsiveness in overweight/obese individuals without apnea is poorly understood. Although a more-effective translation from neuromuscular activity (EMGgg) to increased airflow (e.g., reduced mechanical load, increased muscle strength and coordination, reduced fatigability) may mitigate OSA in many individuals (32–34), our group data indicate that much of the enhanced functional responsiveness (upper-airway gain) in overweight/obese individuals without apnea is neurophysiologic in origin (the EMGgg response to negative pressure). We base this interpretation on the finding that the EMGgg responsiveness is enhanced by a similar magnitude (threefold) as the functional effectiveness (Figure 2 vs. Figure 1B). Enhanced responsiveness may occur at the level of the negative pressure sensory afferents or the medullary negative pressure and CO_2 inputs to the hypoglossal motor nucleus (e.g., via the nucleus of the solitary tract and periobex region [35]). It is also unclear whether the mechanism responsible is inherent (e.g., genetic) or adaptive (e.g., a neuroplastic recalibration of reflexes consequent to weight gain). The absence of large responsiveness values in normal-weight control subjects suggests an adaptive mechanism may be at play that is largely absent in patients with OSA. We also considered the possibility that OSA itself may reduce muscle responsiveness, perhaps by sleep deprivation (36, 37) or neurologic damage (38). However, the current study examined patients with OSA who were treated with CPAP to minimize such effects. Moreover, available evidence suggests that CPAP treatment of OSA has little impact on upper-airway neuromuscular behavior (threshold ventilatory drive required for airway opening) (39). Elucidating the precise mechanism involved may provide for novel therapeutic strategies to enhance muscle responses and treat OSA.

Clinical Implications

Our data illustrate the magnitude of the interventions to the traits that are sufficient for effective OSA resolution in overweight/obese patients with apnea. That is, a threefold increase in dilator muscle responsiveness and an approximately 4 cm H_2O decrease in Pcrit (or increased passive ventilation of ~20% of eupneic levels) should be sufficient to provide patients with apnea with the physiology of individuals without apnea and resolve OSA. We envisage that, in some individuals, OSA treatment could be achieved in this manner by improving anatomy (e.g., with positional therapy or mandibular advancement) in combination with improved muscle responses via novel methods to activate, sensitize, or even train the upper-airway muscles (40–42).

Conclusions

The current study demonstrates that overweight/obese individuals without apnea counteract a moderate anatomic deficit with powerfully enhanced upper-airway dilator muscle responses during sleep to avoid OSA; by contrast there was no evidence of lowered loop gain or elevated arousal threshold compared with patients with OSA. The mechanisms responsible for enhanced responsiveness may provide clues for future treatment. ◼
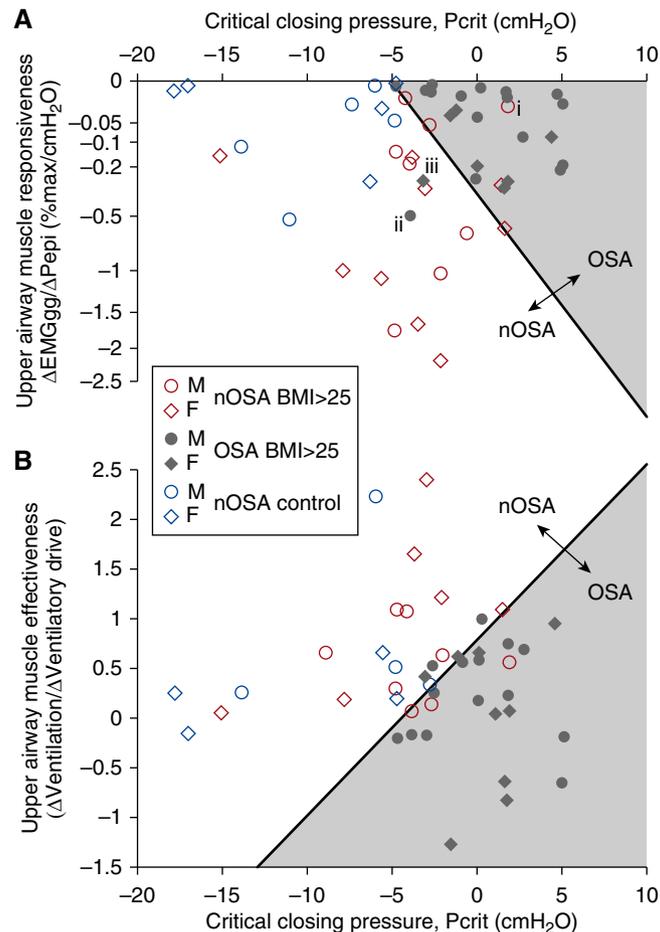
Figure 5. Upper airway collapsibility (Pcrit) and upper airway dilator muscle behavior determine the presence or absence of obstructive sleep apnea (OSA). (*A*) Upper airway responsiveness and Pcrit. (*B*) Upper airway effectiveness (upper airway gain) and Pcrit. Lines based on logistic regression illustrate the boundary between overweight/obese patients with OSA and overweight/obese individuals without OSA. Individuals with more collapsible airways require the most responsive and effective upper airway muscles to avoid OSA. Three outliers are labeled in *A*: (*i*) one individual had minimal responsiveness but avoided OSA likely because of a moderate upper airway effectiveness (+0.6) and very low loop gain (−2), two individuals with good responsiveness developed OSA likely caused by (*ii*) a poor upper airway muscle effectiveness (−0.2) and elevated loop gain (−6), and (*iii*) a low arousal threshold (−8 cm H_2O). Upper airway responsiveness data were square-root transformed to achieve normally distributed data; these data are shown on a square-root scale. Regression models: (*A*) Y = 2.36 + (0.38 × Pcrit) + (3.19 × Responsiveness$^{0.5}$) [Pcrit: *P* = 0.02; Responsiveness: *P* = 0.04], (*B*) Y = 3.31 + (0.63 × Pcrit) − (3.56 × Effectiveness) [Pcrit: *P* = 0.02; Effectiveness: *P* = 0.03]. BMI = body mass index; EMGgg = genioglossus EMG; Pcrit = critical closing pressure.

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