Obstructive sleep apnea without Obesity Is Common and Difficult to Treat: Evidence for a Distinct Pathophysiological Phenotype

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Study Objectives: To determine the proportion and physiological characteristics of nonobese patients with obstructive sleep apnea (OSA) and their response to prescribed therapy.

Methods: Data from 163 consecutive in-laboratory diagnostic sleep studies for participants referred to an academic teaching-hospital sleep clinic for suspected OSA were assessed. Sleep and anthropometric parameters at baseline and follow-up (up to 22 mo) were examined and compared between obese and nonobese patients with a diagnosis of OSA (apnea-hypopnea index > 5 events/h sleep). A key nonanatomical contributor to OSA pathogenesis, the respiratory arousal threshold, was compared between groups.

Results: Twenty-five percent of the participants with a diagnosis of OSA had a body mass index (BMI) within the normal range (BMI < 25 kg/m²) and 54% had a BMI < 30 kg/m² (nonobese). Of the patients prescribed continuous positive airway pressure (CPAP), more nonobese patients reported not using their CPAP machine at all at follow-up (36% vs. 13%, p = 0.03). Objective CPAP compliance was also lower in the nonobese patients with OSA (5.1 ± 0.4 vs. 6.4 ± 0.4 h/night, p < 0.03). A higher proportion of the nonobese patients had a low respiratory arousal threshold compared to obese OSA patients (86% vs. 60%, p < 0.001).

Conclusions: A substantial proportion of patients with OSA are not obese. These patients are challenging to treat with existing therapies as they are less adherent and compliant with CPAP therapy. Nonanatomical contributors to OSA, such as a low threshold for arousal, are likely to be particularly important in OSA pathogenesis in nonobese patients with OSA. These findings have important implications for the pathogenesis of OSA in nonobese patients and potential therapeutic targets for this group of patients.

Keywords: arousal threshold, continuous positive airway pressure therapy, nonobese, sleep apnea pathogenesis, upper airway


INTRODUCTION

Obstructive sleep apnea (OSA) is an increasingly common sleep-related breathing disorder. Indeed, recent estimates indicate that from 3% to 23% of women and 9% to 49% of middle-aged men have moderate to severe sleep-disordered breathing as defined by an apnea-hypopnea index (AHI) > 15 events/h sleep. OSA is characterized by repeated upper airway obstruction during sleep causing acute disruptions to blood oxygen levels, heart rate, blood pressure, intrathoracic pressure, and sleep quality. These immediate effects have long-term sequelae, increasing the risk of hypertension, cardiovascular morbidity, and premature death, as well as causing decrements in cognitive function, mood, and quality of life.

Obesity is a major risk factor for OSA. Surprisingly, however, there is a lack of clinical data on the characteristics and responses to existing therapies in nonobese patients with OSA. Current estimates indicate that nonobese individuals constitute at least 20% of the adult OSA population. Non-obese patients with OSA have an OSA-attributable risk for hypertension greater than fourfold higher than that of obese adults younger than 65 y and odds of early atherosclerosis of 2.7-fold. An initial report indicates that nonobese patients with OSA may be more challenging to treat with existing therapies such as continuous positive airway pressure (CPAP). Thus, there is a need to identify and develop effective alternate therapies for nonobese patients with OSA.

In order to optimize and develop tailored therapeutic approaches for non-obese patients with OSA, improved understanding of the causes of OSA in the absence of obesity is required. OSA is caused by an interaction between anatomical and nonanatomical factors or traits. Nonanatomical traits, present in approximately 70% of all patients with OSA,
include an increased propensity for awakening to respiratory stimuli (low respiratory arousal threshold), unstable ventilatory control (high loop gain) and ineffective upper-airway dilator muscles during sleep. Anatomical factors, such as small craniofacial structures, can lead to a crowded upper airway and increased upper airway collapsibility in certain nonobese patients with OSA. However, few studies have examined the role of nonanatomical contributors to OSA pathogenesis in nonobese patients with OSA. Between 30% to 50% of all patients with OSA have a low respiratory arousal threshold. A recent study showed an association between increasing body mass indices (BMIs) and the respiratory arousal threshold. This finding indicates the potential importance of nonanatomical contributors such as a low arousal threshold to OSA pathogenesis in nonobese patients. Quantification of the arousal threshold and the other nonanatomical traits that cause OSA typically requires time-intensive methodology in which manipulations in CPAP are performed during sleep by an experienced investigator and specialized, invasive recording equipment (e.g., an epiglottic pressure catheter). However, allowing for investigation in clinical cohorts, a simple, accurate tool to estimate the respiratory arousal threshold trait from standard polysomnographic variables has recently been developed. Thus, although it will be important to systematically investigate potential differences in each of the nonanatomical traits that cause OSA between obese and nonobese patients, at this time, only the arousal threshold trait can be estimated noninvasively. Accordingly, this study aimed to define the proportion and physiological characteristics of nonobese individuals and their response to prescribed therapy in a clinical cohort referred for suspected OSA. We hypothesized that nonobese patients with OSA would be less adherent to CPAP and more likely to have nonanatomical causes of OSA (including low respiratory arousal threshold) compared to obese patients with OSA.

METHODS

Participant Information/Study Design
Data from 190 consecutive in-laboratory diagnostic sleep studies collected between January and April 2014 were assessed. One hundred sixty-three studies were performed for individuals referred to an academic teaching hospital sleep clinic for suspected OSA. Following the diagnostic sleep study, all participants were booked to see a sleep physician for clinical follow-up. The study was approved by the South Eastern Sydney Local Health District Human Research Ethics Committee.

Equipment and Measurements
Information on medical history, medications, and smoking use was obtained from questionnaires given to all participants prior to their overnight sleep study. Height and weight were obtained. The Epworth Sleepiness Score (ESS) was used to assess daytime sleepiness.

Each participant was studied overnight using in-laboratory polysomnography (PSG) (Alice Sleepware, Murrysville, PA). Briefly, participants were fitted with standard PSG sleep staging and respiratory monitoring equipment including electroencephalogram (EEG), electrooculography, electrocardiogram, submental and anterior tibialis electromyogram, airflow (nasal pressure and thermistor), oximetry, respiratory effort bands, and a position sensor.

Follow-up data regarding sleep-physician review attendance, recommended therapy, and download data from CPAP usage (where available) were obtained up to 22 mo following the original diagnostic PSG. ‘CPAP usage’ was also defined as the sleep physician stating that the patient was on CPAP treatment in the initial follow-up letter following the treatment recommendation visit. This definition included patients with potential suboptimal usage.

The respiratory arousal threshold is typically quantified using an epiglottic or esophageal pressure catheter as the nadir pressure immediately preceding a cortical arousal from sleep (defined as ≥ 3 sec of high-frequency activity on EEG). A low respiratory arousal threshold is defined as a pressure between 0 and −15 cmH₂O. In the current study, we estimated which patients had a low respiratory arousal threshold according to a recently validated score derived from standard PSG variables. Specifically, a low respiratory arousal threshold was defined as a score of two or more on the following three-point scale: (AHI < 30 events/h sleep) + (nadir SpO₂ > 82.5%) + (fraction of hypopneas > 58.3%). This approach has a high sensitivity (80%) and specificity (88%) in detecting patients with OSA with a low respiratory arousal threshold. Additionally, we estimated the actual arousal threshold values for each participant using the following multiple linear regression model described by Edwards and colleagues: arousal threshold = −65.391 + (0.0636 * Age) + (3.692 * Sex [whereby male = 1, female = 0]) − (0.0314 * BMI) − (0.108 * AHI) + (0.533 * Nadir SpO₂) + (0.0906 * % hypopneas). As a simple alternative measure to estimate the propensity for arousal, we also calculated the fraction of spontaneous arousals to total arousals (Fspont) and compared this parameter between obese and nonobese patients with OSA.

Data Analysis
Normal BMI was defined as < 25 kg/m², overweight as between 25–29.9 kg/m², and obese as ≥ 30 kg/m². Nonobese subjects had a BMI < 30 kg/m². Sleep staging and respiratory events were scored in 30-sec epochs according to the revised version of the American Academy of Sleep Medicine Scoring Manual 2007, by certified sleep technicians blinded to the intent of the study. Hypopneas were defined as a reduction in the nasal pressure excursions by ≥ 30% from the preevent baseline that lasted ≥ 10 sec and were associated with a ≥ 3% oxygen desaturation or a cortical arousal. A diagnosis of OSA was defined as an AHI > 5 events/h of sleep.

Statistical Procedures
Statistical analyses were performed using Prism (v6.05, Graphpad Software Inc., La Jolla, CA). Normality was assessed using the Kolmogorov–Smirnov test. Gaussian variables were expressed as mean ± standard deviation (SD) and non-parametric variables as median ± interquartile range (IQR). Descriptive
variables were expressed as frequencies and percentages. The $\chi^2$ test was used to determine the association between qualitative variables; one-way analysis of variance was used for the gaussian quantitative variables; Fisher exact test was used for categorical variables and Wilcoxon signed-rank tests were used for nonparametric comparisons. Primary comparisons were performed between obese and nonobese patients. Univariate analysis was performed for BMI, age, AHI, estimated arousal threshold, and $F_{spont}$ for reported CPAP usage. Variables found to be significant on univariate analysis were added to a multivariate analysis. A value of $p < 0.05$ was considered statistically significant.

### RESULTS

#### Participants

One hundred ninety consecutive diagnostic sleep studies performed in an academic teaching hospital sleep center were performed between January and April 2014. Individuals who already had a diagnosis of OSA, were pregnant, had neuromuscular disorders, or were suspected of narcolepsy were excluded. Of the 163 remaining study participants, 90% had a diagnosis of OSA (defined as AHI > 5 events/h sleep). Twenty-five percent had a BMI within the normal range (BMI < 25 kg/m$^2$) and 54% had a BMI < 30 kg/m$^2$ (non-obese). Demographic details are shown in Table 1. Individuals of normal weight were younger than both overweight and obese subjects. Overweight subjects were less sleepy as determined by the ESS and obese subjects were more likely to have atrial fibrillation, hypertension, and be current or ex-smokers.

#### OSA Severity

Normal and overweight subjects did not differ in their severity of OSA with similar median AHIs (Figure 1). However, both groups had a significantly lower AHI compared with the obese patients (Figure 1). Accordingly, data for normal and overweight subjects were grouped for further primary analyses.

### Treatment Recommendations

A lower proportion of nonobese compared to obese subjects were offered CPAP therapy at the initial consultation following their diagnostic sleep study (Figure 2). A similar proportion of obese and nonobese patients with OSA did not return for their follow-up appointment (Table 2, Figure 2). Of the 64 patients prescribed CPAP who reported for follow-up post-therapy, machine download data were available in 36 (56%). Nonobese patients tended to be recommended no treatment or non-CPAP therapies more than obese patients, although the proportions were not significantly different between groups ($p = 0.1$, Figure 2). Overall, the clinical and physiological characteristics of the obese and nonobese patients for the various treatment recommendation groups were similar (Table 2).
However, the AHI and the arousal threshold were lower in the nonobese group (Table 2).

### Treatment Take-Up

Of the patients who were prescribed CPAP therapy and returned for follow-up, a higher proportion of nonobese patients reported not using their CPAP at all (36% vs. 13%, p = 0.03). Age, sex, and ESS were not associated with CPAP usage ($r^2$ all < 0.03, $p > 0.25$), whereas BMI and AHI were positively associated ($r^2 = 0.07, p = 0.04$ and $r^2 = 0.10, p = 0.01$, respectively). $F_{\text{spont}}$ and the estimated arousal threshold were negatively associated with CPAP usage on univariate analysis ($r^2 = 0.09, p = 0.02$ and $r^2 = 0.07, p = 0.04$, respectively). However, when the significant variables from the univariate analyses were entered into a multivariate model, only BMI and $F_{\text{spont}}$ remained significant ($model r^2 = 0.13, p = 0.02$).

A substantial proportion of patients did not attend follow-up appointments after they were prescribed CPAP therapy. However, this proportion was not significantly different between groups (25% nonobese vs. 38% obese, $p = 0.07$). The overall CPAP usage rate according to sleep physician documentation at the initial follow-up visit following treatment recommendation for the patients who were offered therapy was 51%. This value includes zero values for each patient who did not return for follow-up.

In the patients who reported for follow-up and in whom machine download data were available, the mean hours of CPAP usage measured objectively was 6.0 ± 1.9 h per night. There was a significant dose response effect such that CPAP compliance increased with increasing BMI category ($p = 0.02$, Figure 3).
CPAP compliance was significantly less for the nonobese compared to the obese patients (5.1 ± 0.4 [n = 17] vs. 6.4 ± 0.4 [n = 19], p = 0.03).

Nonanatomical Causes: Role of Arousal Threshold
A higher proportion of the nonobese patients with OSA were estimated to have a low respiratory arousal threshold (86% nonobese vs. 60% obese, p < 0.001). Using the multiple linear regression model,23 the estimated respiratory arousal threshold in the nonobese compared to the obese group was −15.9 [−14.9 to −16.8] vs. −21.2 [−19.5 to −22.8] cmH.O, p < 0.0001. The Fspont was also higher in the nonobese compared to obese patients with OSA (0.33 [0.20–0.50] vs. 0.28 [0.14–0.42], p = 0.01).

DISCUSSION
The main findings of this study are that a substantial proportion of patients referred for suspected OSA are not obese and these patients are a challenging group to treat with currently available modalities, such as CPAP. In addition, a higher proportion of nonobese patients have a low respiratory arousal threshold, suggesting that nonanatomical causes may be particularly important for the pathogenesis of OSA in the absence of obesity. As discussed in the next paragraphs, these findings have implications for treatment of nonobese patients with OSA.

OSA in the Absence of Obesity is Common
Recent community sample data from more than 1,500 individuals in the Wisconsin sleep cohort indicate that, among the nonobese, almost 5% of men and 1% of women aged 30–49 y have moderate to severe OSA.2 These figures increase to 14% and 5% of nonobese men and women aged 50–70 y.2 Similarly, recent polysomnographic data from a community sample of more than 2,000 individuals aged 40–85 y in Switzerland show very high rates of moderate to severe OSA (23% in women and nearly 50% in men).1 This is despite the cohort having a mean BMI of only 25.6 kg/m².

PSG data collected from 18 sleep centers across the US from 2004 to 20088 indicate that at least one in five patients who underwent a diagnostic sleep study for excessive daytime sleepiness with confirmed OSA (AHI > 5 events/h sleep) had a BMI < 27 kg/m². Over half of these patients had moderate to severe OSA.11 The findings of the current study indicating that 25% of OSA patients have a BMI within the normal range (< 25 kg/m²) and approximately 50% are not obese are consistent with studies by Mortimore and colleagues32 and other clinical referral cohorts.27,28 Thus, OSA is common without obesity in the general community and in sleep clinics.

Clinical Characteristics of Nonobese Patients with OSA
Our data showing that nonobese patients with OSA tend to have less severe OSA compared with obese patients are consistent with previous reports.2,29 Obesity places a mass load on the upper airway and increases its collapsibility.30,31 Indeed, the upper airway is less collapsible in nonobese than obese patients with OSA.18,31 Consistent with increased upper airway collapsibility with age,31,32 patients of normal weight in the current study were younger than the more obese patients with more severe OSA. However, despite known differences in OSA pathophysiology between the sexes, the proportion of men versus women did not differ according to BMI status in the current study.

Treatment Recommendations and Responses
Although proportionally more obese patients with OSA were offered CPAP in the current study, CPAP remained the first-line treatment recommendation regardless of obesity status. Our overall CPAP adherence to prescribed treatment of just over half is in accordance with prior findings indicating that up to 50% of patients in whom CPAP was recommended may not have commenced or lapsed with treatment after 1 to 3 y.33–35 In addition, objective CPAP compliance in the current study is in line with review data suggesting that 29% to 83% of OSA patients average less than 4 h of CPAP usage per night.36 Furthermore, our finding that obese patients with OSA are more likely to comply with CPAP therapy is consistent with recent data from Kim and colleagues.15 Specifically, these authors demonstrated an overall CPAP compliance rate of 61%, with a higher proportion of obese compared to non-obese patients being CPAP compliant at 12 mo (68% vs. 42%).15

The tendency to prescribe no treatment or non-CPAP alternatives in the nonobese patients in the current study is consistent with less severe OSA and less pronounced upper airway anatomical compromise in nonobese patients with OSA. Furthermore, success rates for non-CPAP therapies that target the anatomical trait such as mandibular advancement devices and upper airway surgery, including new hypoglossal nerve stimulation therapy, have been reported to be higher in less obese patients with OSA.37,38 However, efficacy remains variable and difficult to predict based on obesity status alone.39 Thus, as discussed in the following paragraphs, unless the non-anatomical causes of OSA are also addressed, anatomical interventions in isolation that have less of an effect size than CPAP would not be expected to yield therapeutic benefit in all OSA patients.
Nonanatomical Contributions to OSA Pathogenesis in Nonobese Patients and Targeted Treatments

This is the first study to show that a key nonanatomical contributor to OSA pathogenesis, the respiratory arousal threshold, differs in nonobese and obese patients with OSA. A prior study demonstrated that approximately half of all untreated patients with OSA have a low respiratory arousal threshold. A low threshold for arousal to airway narrowing is thought to cause OSA due to the destabilizing effects of repeated arousals by: (1) decreased sleep continuity and prevention of deeper more stable sleep, (2) excessive reductions in partial pressure of carbon dioxide promoting dynamic ventilatory instability, and (3) decreased respiratory drive to the upper airway muscles. Decreased respiratory drive to the upper airway muscles in these “light sleepers”. In accordance with this concept, in patients with lower arousal thresholds, sleep oxygenation was lower in patients with lower arousal thresholds on univariate (but not multivariate) analysis. Additionally, a simple new measure of the propensity for awakening, the fraction of spontaneous arousals to total arousals, was negatively associated with CPAP usage (i.e., CPAP usage was lower in patients with lower arousal thresholds). The current findings indicating that as many as 9 of 10 nonobese patients with OSA have a low threshold supports a study on the effects of sleep-promoting agents in nonobese patients with OSA.

A low respiratory arousal threshold phenotype may also be a physiological factor that limits CPAP tolerance in many nonobese patients and contributes, at least in part, to poor CPAP compliance in these patients. Specifically, the mask and positive airway pressure may further contribute to sleep disruption in these “light sleepers”. In accordance with this concept, in the current study we found that the estimated arousal threshold was negatively associated with CPAP usage (i.e., CPAP usage was lower in patients with lower arousal thresholds) on univariate (but not multivariate) analysis. Additionally, a simple new measure of the propensity for awakening, the fraction of spontaneous arousals to total arousals, was higher in nonobese compared to obese patients and this parameter was negatively associated with CPAP usage in univariate and multivariate analyses.

The other nonanatomical traits that cause OSA may also be more common in nonobese patients. Indeed, impaired genioglossus muscle endurance (fatigue) in vitro has been demonstrated in an earlier study in nonobese compared to obese patients with OSA. Unstable ventilatory control may also be more common in nonobese individuals. However, this has not been studied. Thus, there is a need to determine, using the latest phenotyping methodology, if the other key nonanatomical traits are systematically impaired in nonobese patients with OSA. If so, this would provide much-needed new targets for therapy.

Methodological Considerations

The current study design that involved analysis of diagnostic and follow-up data from a cohort of consecutive patients referred for suspected OSA to our academic teaching hospital has multiple strengths. However, several limitations need to be acknowledged. First, we did not formally document the racial background our study population. However, the cohort was predominantly Caucasian. Thus, our findings are not likely to be generalizable to other ethnic groups such as Asian populations in whom BMI obesity cutoffs as well as craniofacial profiles differ. This is a priority for future investigation. Second, although these findings are clinically relevant, the local referral patterns to our sleep center may differ from other centers, more broadly limiting generalizability to other sleep centers and OSA phenotypes in nonobese patients. However, the proportion of nonobese patients with OSA that we report is in line with other sleep centers in the United States and Europe.

Third, the number of nights per week that patients used their CPAP machine was not documented. Sleep physician-documented ‘CPAP usage’ also potentially included suboptimal use. Thus, although the average hours of CPAP usage per night from download data were obtained in a proportion of our clinical cohort, it will be important to objectively quantify CPAP usage, including number of nights of usage per week, in as many patients as possible in future studies. Finally, we used indirect estimates of the respiratory arousal threshold rather than quantification using an epiglottic or esophageal catheter. However, this approach has a high sensitivity (80%) and specificity (88%) in detecting OSA patients with a low respiratory arousal threshold and has greater appeal in terms of its clinical utility. In addition, consistent with the current findings, the arousal threshold measured via an epiglottic pressure catheter in the recent study by Edwards and colleagues was −15.5 [−9.4 to −24.3] vs. −11.2 [−8.3 to −17.3] cmH₂O, p = 0.01 in the obese (46.5% of patients) versus nonobese (53.5% of patients). This is similar to the estimated −5 cmH₂O difference in arousal threshold between obese and nonobese participants reported in the current study. Nonetheless, future investigation of the arousal threshold and the other nonanatomical traits that cause OSA in appropriately designed studies in nonobese patients with OSA using the gold standard approaches is required to confirm and expand upon the novel findings reported here.

Summary and Implications for Clinical Practice

A substantial proportion of OSA patients are not obese. Nonobese patients with OSA are a challenging group to treat with existing therapies; these patients are less adherent and compliant with CPAP therapy compared to obese patients with OSA. Our data also indicate that a key nonanatomical contributor to OSA pathogenesis, a low threshold for arousal, is likely to be particularly important in the pathogenesis of OSA in nonobese patients with OSA. A greater propensity for awakening in nonobese patients with OSA may also be a physiological factor contributing, at least in part, to poor CPAP tolerance in these patients. These findings have important implications for the treatment of OSA in nonobese individuals. Specifically, targeted non-anatomical interventions (e.g., nonmyorelaxant sedatives) to increase the threshold for arousal alone or in combination with existing therapies (e.g., CPAP or oral appliances) may yield greater therapeutic success in this group of patients.

Abbreviations

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<tr>
<td>AHI</td>
<td>apnea-hypopnea index</td>
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<td>BMI</td>
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<td>CPAP</td>
<td>continuous positive airway pressure therapy</td>
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<td>Epworth sleepiness score</td>
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<td>Fspont</td>
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OSA, obstructive sleep apnea
PSG, polysomnography
SpO₂, arterial blood oxygen saturation

REFERENCES


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