

# The Heterogeneity of Obstructive Sleep Apnea (Predominant Obstructive vs Pure Obstructive Apnea)

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**Study Objectives:** To compare the breathing instability and upper airway collapsibility between patients with pure OSA (i.e. 100% of apneas are obstructive) and patients with predominant OSA (i.e., coexisting obstructive and central apneas).

**Design:** A cross-sectional study with data scored by a fellow being blinded to the subjects' classification. The results were compared between the 2 groups with unpaired student *t*-test.

**Setting and interventions:** Standard polysomnography technique was used to document sleep-wake state. Ventilator in pressure support mode was used to introduce hypocapnic apnea during CO<sub>2</sub> reserve measurement. CPAP with both positive and negative pressures was used to produce obstructive apnea during upper airway collapsibility measurement.

**Participants:** 21 patients with OSA: 12 with coexisting central/mixed apneas and hypopneas (28% ± 6% of total), and 9 had pure OSA.

**Measurements:** The upper airway collapsibility was measured by assessing the critical closing pressure (Pcrit). Breathing stability was assessed by measuring CO<sub>2</sub> reserve (i.e., ΔPCO<sub>2</sub> [eupnea-apnea threshold]) during NREM sleep.

**Results:** There was no difference in Pcrit between the 2 groups (pure OSA vs. predominant OSA: 2.0 ± 0.4 vs. 2.7 ± 0.4 cm H<sub>2</sub>O, P = 0.27); but the CO<sub>2</sub> reserve was significantly smaller in predominant OSA group (1.6 ± 0.7 mm Hg) than the pure OSA group (3.8 ± 0.6 mm Hg) (P = 0.02).

**Conclusions:** The present data indicate that breathing stability rather than upper airway collapsibility distinguishes OSA patients with a combination of obstructive and central events from those with pure OSA.

**Keywords:** CO<sub>2</sub> reserve, Pcrit, OSA

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## INTRODUCTION

Since obstructive sleep apnea (OSA) is characterized by futile respiratory efforts against a closed upper airway, patients with OSA are believed to have anatomical/functional deficits in the upper airway (UAW). However, patients very rarely present with pure OSA in clinical practice, with most OSA patients exhibiting some proportion of central and/or mixed events. It is not clear why both types of apnea occur in the same individual during the same night, but the coexistence of two types of apnea indicates more complicated underlying disorders than increased UAW resistance alone. In fact, unstable breathing control has been implicated in the pathogenesis of both central and obstructive sleep apnea. Some patients with OSA exhibit evidence of unstable ventilatory control (i.e., increased control system "loop gain,") that could contribute to UAW narrowing and obstruction.<sup>1,2</sup> We have noticed that obstructive apnea (OA) begins at the nadir of respiratory drive,<sup>3</sup> and that superimposing an unstable respiratory motor output precipitated airway obstruction during sleep in snoring subjects.<sup>4</sup> We have also observed that increasing chemoreceptor stimulation (via increased inhalation of CO<sub>2</sub>) reduced UAW resistance in sleeping subjects.<sup>5</sup> Hence the occurrence of OA appears to involve aspects of both upper airway collapsibility

and respiratory control instability.<sup>2,6</sup> On the other hand, when the central respiratory output drops to zero, central apnea (CA) occurs regardless of UAW structural and functional status. It is very likely that the phenotype of sleep apnea (CA vs. OA) is shaped by the interaction of respiratory drive and UAW resistance. We therefore hypothesized that for patients with equally severe OSA, those with pure OSA have a more collapsible airway than those with coexisting obstructive and central apneas (predominant OSA); while the predominant OSA group have more significant instability of the respiratory system than the pure OSA group. To test this hypothesis, we measured CO<sub>2</sub> reserve (i.e., ΔPCO<sub>2</sub> [eupnea-apneic threshold]) to approximate the breathing propensity for instability and UAW critical closing pressure (Pcrit) to assess the UAW collapsibility in patients with OSA, and compared these 2 indexes between the 2 subgroups (pure OSA vs. predominant OSA).

## METHODS

### Subjects

We studied 21 patients with OSA diagnosed via overnight polysomnography (i.e. all patients had an apnea/hypopnea index [AHI] > 10/h of sleep time). Of the apneas, ≥ 50% were classified as obstructive in nature. Among these 21 subjects, 9 presented with pure OSA (100% of apneas were obstructive) and 12 with predominant OSA (100% > obstructive apneas > 50%). Subjects were excluded if they had chronic obstructive pulmonary disease/asthma, concomitant medical illness such as renal/liver dysfunction, or other confounding sleep disorders. All subjects provided informed consent prior to participation. The experimental protocol was approved by the University of Wisconsin Center for Health Sciences Human Subjects Committee.

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**Table 1—Subject description**

	Pure OSA group	Predominant OSA group	P-value
Number	9 (2 F + 7 M)	12 (1 F + 11 M)	N/A
Age, y	50.6 ± 3.8	54.1 ± 2.6	0.40
BMI, kg/m <sup>2</sup>	36.8 ± 2.8	34.3 ± 1.7	0.43
AHI, events/h	49.2 ± 9.4	47.1 ± 10.4	0.89
AHI in NREM, events/h	45.9 ± 9.3	45.7 ± 9.4	0.75
AHI in REM, events/h	57.0 ± 13.1	50.2 ± 16.3	0.77
AHI in supine, events/h	51.4 ± 12.2	61.6 ± 16.1	0.64
Obstructive apnea (% of total AH events)	27.7 ± 14.4	21.5 ± 7.0	0.67
Central apnea (% of total AH events)	0 ± 0	11.4 ± 6.3	N/A
Mixed apnea (% of total AH events)	0 ± 0	11.8 ± 6.0	N/A
Obstructive hypopnea (% of total AH events)	72.3 ± 14.4	50.6 ± 11.6	0.26
Central hypopnea (% of total AH events)	0 ± 0	4.7 ± 4.7	N/A

BMI, body mass index; AHI, apnea-hypopnea index.

The experiment was completed within 2 weeks following the diagnostic study before the subjects received any treatment. All patients reported to the laboratory in the evening, having refrained from alcohol and caffeinated beverages during or after their evening meal. Zolpidem 10 mg was given prior to bed to facilitate sleep and to suppress the arousability from sleep for purpose of measuring Pcrit and apneic threshold.

### Experimental Set-Up

Subjects slept with a full face mask, through which they were connected to a breathing circuit that could be directed to either a positive pressure source (ventilator) (1~25 cm H<sub>2</sub>O) or an adjustable negative pressure source (-1~-10 cm H<sub>2</sub>O) from wall suction. A 200 liter capacitance was placed in the inflow port to maintain the level of negative pressure applied to the mask nearly constant during the respiratory cycle. The positive pressure source and vacuum source were attached to the inspiratory circuit through T-tubing, which was easily switched from one to the other.

### Polysomnographic Methods and Respiratory Monitoring

Standard polysomnography technique was used to document the sleep-wake state.<sup>7</sup> In addition, ventilation was measured with a pneumotachograph (Model 3700, Hans Rudolph). Nasal/mask pressure was measured with a differential pressure transducer (DP 103, Validyne) from a side port on the mask. Calibrated respiratory inductive plethysmography (Inductotrace, Ambulatory Monitoring Inc.) was used to assess respiratory effort. End-tidal PCO<sub>2</sub> (P<sub>ET</sub>CO<sub>2</sub>) was measured by a gas analyzer (AMETEK, Model CD-3A), which was calibrated by known gases.

### Hypocapnic Apnea Threshold and CO<sub>2</sub> Reserve

Breathing stability during NREM sleep was assessed by measuring the CO<sub>2</sub> reserve (i.e., the proximity between eupneic PCO<sub>2</sub> and apneic threshold PCO<sub>2</sub>).<sup>8</sup> First we administered sufficient

positive airway pressure (CPAP) to eliminate airway obstruction and stabilize breathing. Then we administered pressure support ventilation in a step-wise fashion by increasing the pressure by 2 cm H<sub>2</sub>O every 1 min until apnea and periodic breathing occurred. We confirmed this apneic threshold P<sub>ET</sub>CO<sub>2</sub> by abruptly increasing pressure to the previously determined level in one step.

### Upper Airway Critical Closing Pressure (Pcrit)

Measurements of Pcrit were performed in a standard supine posture with the head positioned in a contoured pillow to assure a constant position. During stable NREM sleep, CPAP was increased by 2 cm H<sub>2</sub>O every 1 min until flow limitation was eliminated, and this *holding pressure* was then maintained throughout the study. For each trial, nasal pressure was lowered from the holding pressure by 1 cm H<sub>2</sub>O for 4-6 breaths and then returned to holding pressure for 1 min before dropping to the next level. This sequence was repeated until airflow ceased (absolute Pcrit) or arousal occurred.

### Data Analysis

For the CO<sub>2</sub> reserve assessment, central apnea was defined as absence of airflow and respiratory effort for ≥ 10 sec. The apnea threshold was determined by averaging the P<sub>ET</sub>CO<sub>2</sub> of the 3 consecutive breaths immediately preceding the apnea.<sup>8</sup> The difference between eupneic P<sub>ET</sub>CO<sub>2</sub> during stable breathing and the apneic threshold P<sub>ET</sub>CO<sub>2</sub> was calculated as the CO<sub>2</sub> reserve.

The absolute Pcrit was defined as the level of mask pressure at which inspiratory airflow first ceased. We were able to obtain this in 18 of 21 subjects. In addition, in all subjects, we obtained a derived Pcrit as determined from peak inspiratory flow-UAW pressure relationships. Peak inspiratory flow of the 3rd through 5th breaths with unambiguous flow limitation during reduction in CPAP was averaged at each level of mask pressure. Pcrit was derived by the zero-flow intercept from the least-square linear regression of maximal flow vs. mask pressure as previously described.<sup>9</sup> All data were collected only from flow-limited breaths with no associated arousal.

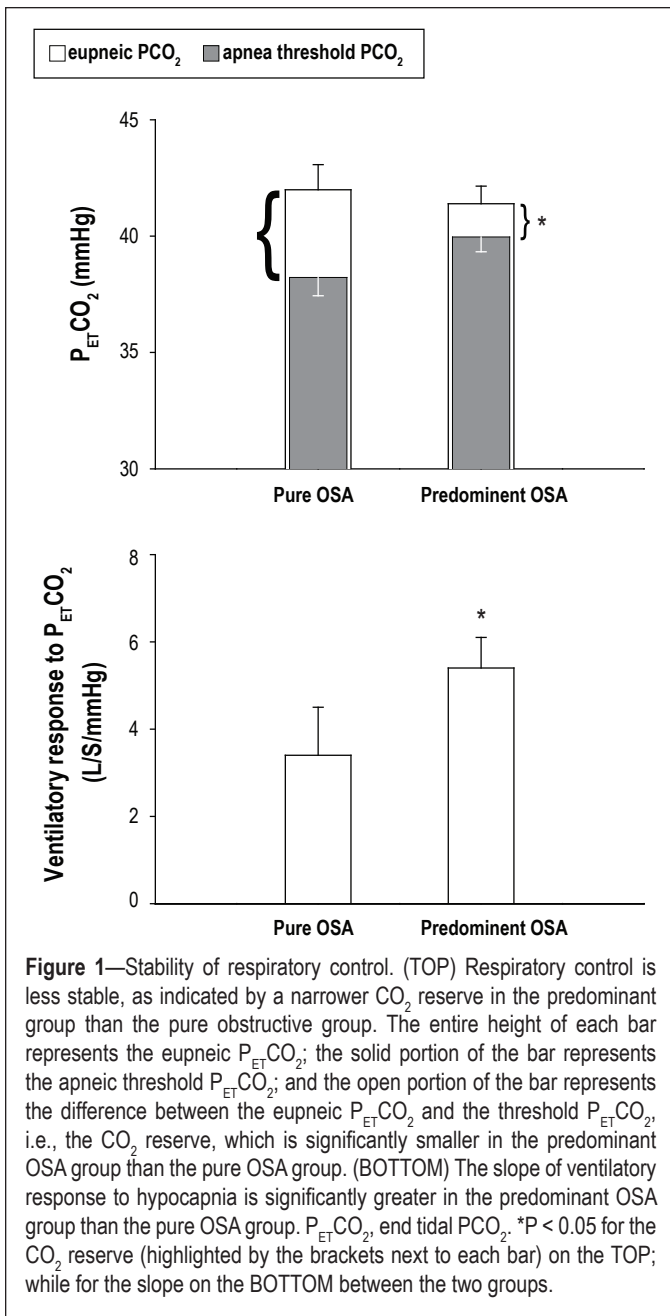
Unpaired *t*-test was used for all of comparisons between the 2 groups. All data are expressed as mean ± SE.

### RESULTS

As Table 1 shows, there was no difference in age, body mass index (BMI), or AHI between the 2 groups. Subjects in both groups were above middle age and overweight. They had moderate to severe sleep apnea syndrome (mean AHI 47-49 events/h of sleep), which was distributed similarly between the 2 groups in terms of sleep stage (45.9 ± 9.3 vs. 45.7 ± 9.4 events/h in NREM sleep, P = 0.75; 57.0 ± 13.1 vs. 50.2 ± 16.3, P = 0.77 in REM sleep) and sleep position (AHI in supine position 51.4 ± 12.2 vs. 61.6 ± 16.1 events/h, P = 0.64). The only difference, by design, was the percentage of central and mixed apneas in the 2 groups, which was 0% in the pure OSA group versus 28.2% ± 6.3% in the predominant OSA group.

### P<sub>ET</sub>CO<sub>2</sub> and CO<sub>2</sub> Reserve

The 2 subgroups had a similar eupneic P<sub>ET</sub>CO<sub>2</sub> during both wakefulness (predominant vs. pure OSA group: 40.4 ± 1.4 vs. 39.8 ± 0.6 mm Hg, P = 0.78) and sleep (41.5 ± 0.9 vs. 42.1 ± 1.0 mm Hg, P = 0.65). Both groups underwent a slight increase in

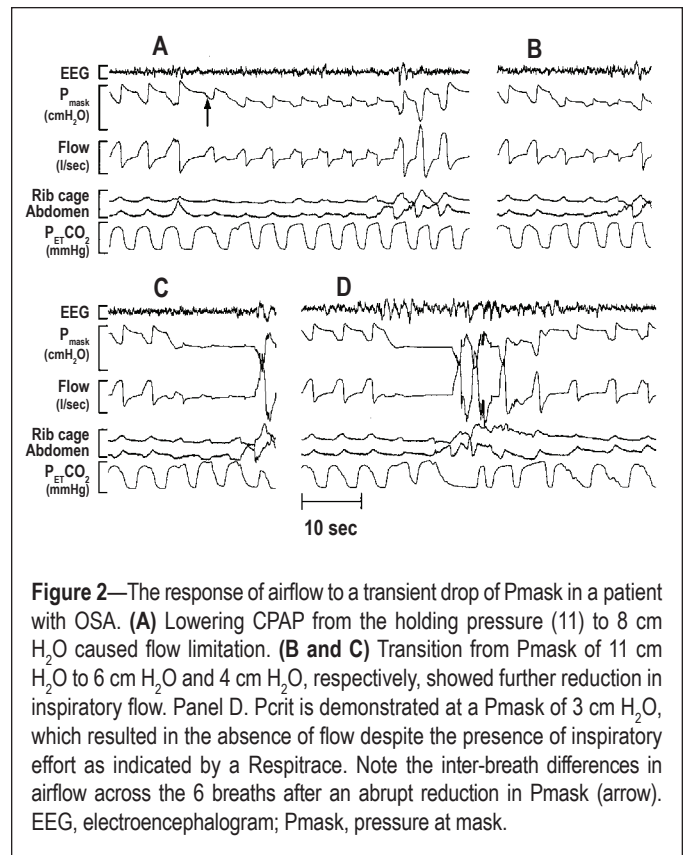


**Figure 1**—Stability of respiratory control. (TOP) Respiratory control is less stable, as indicated by a narrower CO<sub>2</sub> reserve in the predominant group than the pure obstructive group. The entire height of each bar represents the eupneic P<sub>ET</sub>CO<sub>2</sub>; the solid portion of the bar represents the apneic threshold P<sub>ET</sub>CO<sub>2</sub>; and the open portion of the bar represents the difference between the eupneic P<sub>ET</sub>CO<sub>2</sub> and the threshold P<sub>ET</sub>CO<sub>2</sub>, i.e., the CO<sub>2</sub> reserve, which is significantly smaller in the predominant OSA group than the pure OSA group. (BOTTOM) The slope of ventilatory response to hypocapnia is significantly greater in the predominant OSA group than the pure OSA group. P<sub>ET</sub>CO<sub>2</sub>, end tidal PCO<sub>2</sub>; \*P < 0.05 for the CO<sub>2</sub> reserve (highlighted by the brackets next to each bar) on the TOP; while for the slope on the BOTTOM between the two groups.

P<sub>ET</sub>CO<sub>2</sub> from wakefulness to sleep (1.2 ± 1.0 vs. 1.6 ± 1.5 mm Hg, P = 0.84). However, the CO<sub>2</sub> reserve (i.e., the difference between the eupneic P<sub>ET</sub>CO<sub>2</sub> and the apneic threshold P<sub>ET</sub>CO<sub>2</sub>) was significantly smaller in the predominant OSA group (1.6 ± 0.7 mm Hg) than the pure group (3.8 ± 0.6 mm Hg, P = 0.019; Figure 1, top). The reduced CO<sub>2</sub> reserve in the predominant OSA group was due primarily to an increased controller gain below eupnea. The slope of  $\Delta V_E / \Delta P_{ET}CO_2$  in the predominant group vs. pure group was 5.4 ± 0.7 vs. 3.4 ± 1.1 L/min/mm Hg, P = 0.025 (Figure 1, bottom). The severity of sleep apnea (AHI) was moderately correlated to the CO<sub>2</sub> reserve in predominant OSA group (r<sup>2</sup> = 0.61, P = 0.03) but not correlated to the CO<sub>2</sub> reserve in the pure OSA group (r<sup>2</sup> = 0.31, P = 0.42).

### Respiratory Flow Limitation and Pcrit

Most subjects showed various degrees of flow limitation during sleep at atmospheric pressure, which was often but not al-



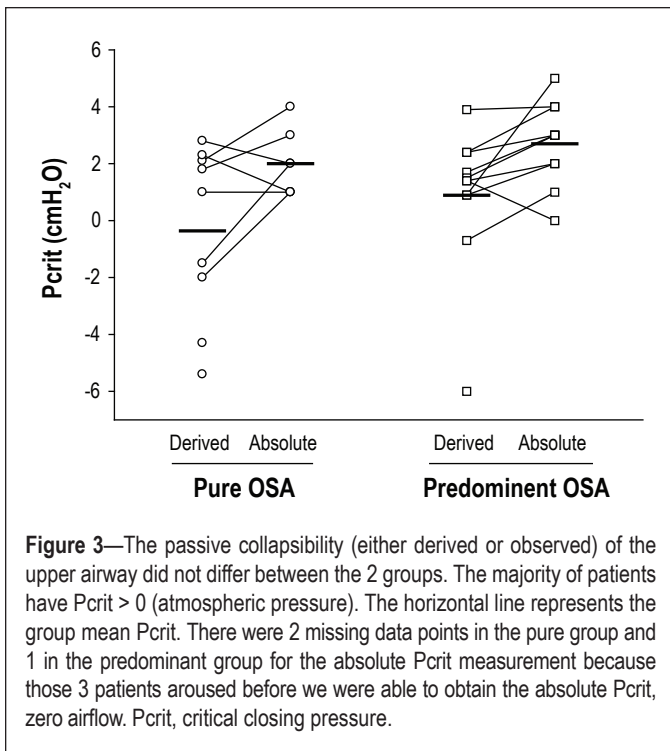
**Figure 2**—The response of airflow to a transient drop of P<sub>mask</sub> in a patient with OSA. (A) Lowering CPAP from the holding pressure (11) to 8 cm H<sub>2</sub>O caused flow limitation. (B and C) Transition from P<sub>mask</sub> of 11 cm H<sub>2</sub>O to 6 cm H<sub>2</sub>O and 4 cm H<sub>2</sub>O, respectively, showed further reduction in inspiratory flow. Panel D. P<sub>crit</sub> is demonstrated at a P<sub>mask</sub> of 3 cm H<sub>2</sub>O, which resulted in the absence of flow despite the presence of inspiratory effort as indicated by a Resptrace. Note the inter-breath differences in airflow across the 6 breaths after an abrupt reduction in P<sub>mask</sub> (arrow). EEG, electroencephalogram; P<sub>mask</sub>, pressure at mask.

ways associated with snoring. The minimum positive pressure required to normalize the airflow (i.e., holding pressure) was 10.0 ± 0.6 cm H<sub>2</sub>O in the pure OSA group and 11.6 ± 0.6 in the predominant OSA group; the difference was not significant (P = 0.07).

We were able to obtain absolute P<sub>crit</sub> on 7 of 9 patients in the pure OSA group and on 11 of 12 patients in the predominant OSA group. For each individual, the absolute P<sub>crit</sub> over 2-4 repeat trials varied within 2 cm H<sub>2</sub>O between the maximum and minimum values in most (16 of 18) patients. The other 3 patients aroused before we obtained zero flow. Their derived P<sub>crit</sub> was about -5~-6 cm H<sub>2</sub>O.

Figure 2 shows the response of airflow to a transient drop of mask pressure in a patient with OSA. Lowering CPAP from the holding pressure progressively caused more and more severe flow limitation and reduction in inspiratory flow (Panels A to C). A further drop of CPAP from 11 cm H<sub>2</sub>O to 3 cm H<sub>2</sub>O resulted in the absence of flow despite the presence of inspiratory effort as indicated by Resptrace, which was defined as absolute P<sub>crit</sub>. When examining the breaths following the abrupt reduction of CPAP, we noticed that the 1st-2nd breath almost always had less flow limitation and less reduction of flow rate than the ensuing 2-4 breaths, while there was little inter-breath difference in airflow across the 3rd-6th breaths.

As Figure 3 shows, most patients had an absolute P<sub>crit</sub> between 1 and 3 cm H<sub>2</sub>O. The mean absolute P<sub>crit</sub> was 2.0 ± 0.4 cm H<sub>2</sub>O in the pure OSA group and 2.7 ± 0.4 cm H<sub>2</sub>O in the predominant OSA group, and there was no significant difference between the 2 groups (P = 0.27). The derived P<sub>crit</sub> was -0.36 ± 1.0 cm H<sub>2</sub>O in the pure OSA group and 0.89 ± 0.77 cm H<sub>2</sub>O in the predominant OSA group, and the difference was also not significant (P = 0.33).



**Figure 3**—The passive collapsibility (either derived or observed) of the upper airway did not differ between the 2 groups. The majority of patients have Pcrit > 0 (atmospheric pressure). The horizontal line represents the group mean Pcrit. There were 2 missing data points in the pure group and 1 in the predominant group for the absolute Pcrit measurement because those 3 patients aroused before we were able to obtain the absolute Pcrit, zero airflow. Pcrit, critical closing pressure.

## DISCUSSION

This study demonstrated that in clinically diagnosed OSA patients, those with a combination of central, mixed, and obstructive apneas had a steeper slope of ventilatory response to  $\Delta P_{ET} CO_2$  below eupnea and a narrower  $CO_2$  reserve relative to the pure OSA patients. On the other hand, passive collapsibility of the upper airway did not differ between the two groups, as they both showed a similar elevation of Pcrit above atmosphere pressure. These findings indicate that (1) increased upper airway collapsibility is commonly seen in most patients in both phenotypes of OSA and (2) neurochemical control instability more likely contributes to the sleep disordered breathing in patients with a combination of central and obstructive apneas.

## Methodological Concerns

We quantified the propensity for respiratory control instability and sleep apnea by measuring  $CO_2$  reserve (i.e., the difference in  $PCO_2$  between eupnea and the apneic threshold). With the withdrawal of wakeful influences breathing becomes critically dependent on  $CO_2$ , as shown by the unmasking of a highly sensitive hypocapnic-induced apneic threshold in NREM sleep.<sup>10,11</sup> Unstable and often periodic breathing patterns during sleep have been shown to occur when the  $CO_2$  reserve is narrowed.<sup>8,12,13</sup> In turn, a reduced  $CO_2$  reserve occurs when controller gain (slope of the  $CO_2$  ventilatory response below and/or above eupnea) and/or plant gain (change in  $V_A$  required to reach the apneic threshold)<sup>14-16</sup> are increased, as demonstrated in patients with heart failure<sup>17</sup> or experimentally in hypoxic environments.<sup>8,12</sup> Therefore, the  $CO_2$  reserve presents an index of breathing control stability, that is, the greater the slope of the  $CO_2$  ventilatory response, the closer the proximity of eupneic  $P_{ET} CO_2$  to apnea threshold  $P_{ET} CO_2$ , and the less stable the control system.<sup>15</sup>

To examine the propensity for upper airway collapsibility, Pcrit was measured after the method of Schwartz et al.<sup>18</sup> Fol-

lowing the reduction in CPAP from holding pressure, we and others<sup>9</sup> observed the greatest increase in flow resistance over the subsequent third to fifth breath. Accordingly, we used these breaths to determine the derived Pcrit. We used the Pcrit obtained by this method as an index of a patient's inherent airway collapsibility.<sup>19,20</sup> However, we could not rule out the influence on Pcrit from variations in lung inflation and/or airway tonicity.<sup>21</sup> Finally, we did observe that the "derived" Pcrit (from pressure-flow regression) was less than the "absolute" Pcrit (at observed zero flow); however, both measurements of Pcrit were nearly identical in the pure OSA group and combined central/obstructive patient group.

We used a mild sedative medication, 10 mg of zolpidem, during the Pcrit and apnea threshold measurement to facilitate sleep and suppress the arousability from sleep. The combination of solid sleep, mild sedation, and high level of nasal CPAP should create a relatively hypotonic state in the UAW muscles. Since both groups of patients used the same dosage of zolpidem, its effect, if any, on the Pcrit and  $CO_2$  reserve should not affect our conclusion. All data were collected during stage 2-3 NREM sleep in the supine position to avoid any influence of sleep states or body position on the Pcrit measurements.

## Causes/Implications of the Elevated Pcrit in OSA Patients

Both pure OSA patients and the combined central/obstructive patient groups showed a positive Pcrit (2-2.3 cm  $H_2O$ ) and required higher CPAP holding pressures (10-11 cm  $H_2O$ ) to ensure airway patency compared to normal individuals.<sup>22-24</sup> These data suggest a highly collapsible UAW in all OSA patients. Our study did not examine the causes of increased passive collapsibility of the airway in each individual. However, our patients did have a significantly increased body mass, which may partially account for the elevation of Pcrit because fat deposition in the airway wall and fatty infiltration of the tongue would increase the soft tissue mass.<sup>25</sup> Moreover, obesity reduces resting lung volume, resulting in loss of caudal traction on upper airway structures and parallel increases in pharyngeal collapsibility.<sup>26</sup> The positive Pcrit predisposes them to UAW occlusion during sleep even with the normal decline in pharyngeal dilator muscle activity that occurs upon withdrawal of the wakefulness stimulus.<sup>27</sup>

## Reduced $CO_2$ Reserve in the Combined Central/Obstructive Group

Our combined central/obstructive apnea patients differed from the pure OSA patient group primarily in showing a steeper ventilatory response slope to  $CO_2$  below eupnea, thereby causing a narrower reserve of  $PaCO_2$  between eupnea and the apneic threshold, i.e., less breathing control stability. Unstable ventilation and increased control system loop gain have been linked to OSA in several clinical and experimental studies.<sup>1-6</sup>

Why and how does respiratory instability predispose to obstructive events? It is known that maintenance of pharyngeal patency requires sufficient neuromotor activation of the UAW dilator muscles to offset the negative intraluminal pressure during inspiration and/or to prevent passive airway collapsibility at end-expiration. The UAW muscles are modulated by the respiratory control system,<sup>28,29</sup> so that the upper airway resis-

tance is inversely correlated with the intensity of the respiratory drive.<sup>5,30</sup> The high chemosensitivity in the predominant OSA group patients means that the respiratory control system will over-respond to a given set of chemoreceptor stimuli (likely to an excess ventilatory response at apnea termination and/or apnea in response to relatively small reductions in PaCO<sub>2</sub>). When the apneic threshold is very close to the spontaneously breathing PCO<sub>2</sub>, as seen in the predominant OSA group, hyperpneas very easily drive PaCO<sub>2</sub> below apneic threshold, resulting in a temporary cessation of the respiratory drive. Airway imaging studies revealed that airway narrowing or closure often occurs early after the onset of a “central” apnea and even in the absence of inspiratory effort.<sup>3</sup> Furthermore, transient hypocapnia may decrease hypoglossal nerve activity more than phrenic nerve activity, causing an imbalance in the activity of pump vs. upper airway muscle activities.<sup>31</sup> In addition, since OSA patients have their pharyngeal patency more sensitive to withdrawal of ventilatory drive than normal individuals,<sup>30</sup> they are expected to be more vulnerable to breathing instability, and any respiratory fluctuations readily predisposes their upper airways to occlusion. This tendency is especially true in individuals with Pcrit close to atmospheric pressure,<sup>32</sup> as seen in most of our subjects.

We emphasize that our study has only examined two factors, i.e., chemosensitivity and UAW collapsibility, as significant contributors to OSA. However, many other factors such as arousability and recruitability of upper airway dilator muscle are also important in determining the breathing pattern and type of apneas.<sup>33-35</sup> This is further complicated by the fact that chemosensitivity will also play an important role in determining both arousability and muscle recruitment ability.

## SUMMARY

The major finding of this study is that quantitative differences in CO<sub>2</sub> reserve, reflecting differences in the propensity for respiratory control stability, distinguishes combined central/obstructive OSA from pure OSA. The present study also emphasizes the equally elevated Pcrit in the two groups, indicating that upper airway collapsibility is a universal problem for all types of OSA patients. Since the majority of OSA patients have some degree of coexisting central events, our observations suggest that central respiratory instability and upper airway collapsibility act synergistically in contributing to OSA, at least in most OSA patients. These observations deepened our understanding of the importance of heteropathy for each phenotype of OSA and may offer new therapeutic options for the treatment of refractory OSA. We would predict, for example, that stabilization of breathing pattern would reduce AHI in certain types of OSA patients. Further work is required to determine how these variables interact, and whether treatment of central system stability in some OSA patients may also relieve a significant number of obstructive events.

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## DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.

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