# Respiratory Determinants of Diurnal Hypercapnia in Obesity Hypoventilation Syndrome

## What Does Weight Have to Do with It?

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## Abstract

**Rationale:** Among morbidly obese individuals, obstructive sleep apnea (OSA) is highly prevalent, with up to 20% suffering from hypoventilation syndrome. An increased diurnal $Pa_{CO_2}$, the signature of obesity hypoventilation syndrome (OHS), implies diminished global ventilation, hence the term hypoventilation.

**Objectives:** We hypothesized that hypercapnic patients with OSA have lower $\dot{V}_E$ than eucapnic patients with OSA.

**Methods:** In this prospective study we recorded respiratory variables to determine the pathophysiological mechanisms of steady-state diurnal hypercapnia of 12 consecutive hypercapnic and 20 consecutive eucapnic patients with OSA, matched for apnea–hypopnea index. Patients with any known causes of hypercapnia were not included.

**Measurements and Main Results:** Comparing hypercapnic to eucapnic patients, the mean value (±SD) for $Pa_{CO_2}$ (52 ± 5 vs. 40 ± 3 mm Hg) was significantly higher, and the mean $Pa_{O_2}$ (59 ± 8 vs. 75 ± 10 mm Hg) was significantly lower, in the hypercapnic patients. Surprisingly, the mean values for $\dot{V}_E$ (12.2 ± 3.0 vs. 11.6 ± 2.0 L/min), alveolar ventilation, breathing rate, $\dot{V}_T$, and dead space did not differ significantly. However, hypercapnic patients had a significantly greater $CO_2$ production (336 ± 79 vs. 278 ± 58 ml/min), which was the main reason for hypercapnia. When adjusted for body surface area, the mean values for $CO_2$ production were similar between the two groups.

**Conclusions:** These data emphasize the importance of weight loss, which could potentially reverse hypercapnic OSA to eucapnic OSA, hypothetically even in the absence of improvement in apnea–hypopnea index. In addition, reversal of hypercapnia should also improve oxygenation, both during sleep and while awake, minimizing hypoxia-induced organ dysfunction of OHS.

**Keywords:** metabolic rate; weight loss; morbid obesity; hypoxia; $CO_2$ retention

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Obesity is a highly prevalent disorder associated with excess health cost and multiple medical complications. One of these consequences, obesity hypoventilation syndrome (OHS), is a distinct clinical entity characterized by the combination of obesity, daytime steady-state hypercapnia, and the presence of a sleeping breathing disorder, usually, although not always, obstructive sleep apnea (OSA) (1–7). Hypercapnia should not be due to other known diseases.

OHS is associated with a number of comorbidities and in the long run with premature mortality. A major consequence of hypercapnia is the imposed hypoxemia, which contributes to inflammation and organ dysfunction in patients with OHS.

Although the term hypoventilation defines the syndrome by referring to the elevated $Pa_{CO_2}$, to our knowledge, there are no systematic studies defining the respiratory determinants of diurnal hypercapnia. In general, when the term hypercapnia is used, it implies diminished global ventilation, hence the term hypoventilation. Although this is the case in some conditions associated with hypercapnia (8), for example opioid-induced respiratory depression when global ventilation and therefore alveolar ventilation is diminished, hypercapnia could be present despite normal global ventilation (8–10).

Equation 1 is the simple formula of alveolar ventilation showing that $Pa_{CO_2}$ is directly proportional to $CO_2$ production ($\dot{V}co_2$) and inversely proportional to alveolar ventilation ($\dot{V}A$):

$$Pa_{CO_2} = K \times \dot{V}co_2/\dot{V}A, \qquad (1)$$

where K is a constant.

Because $\dot{V}A = \dot{V}E$ minus dead space ventilation ($V_D$), the denominator of the equation is changed and:

$$Pa_{CO_2} = K \times \dot{V}co_2/MV - \dot{V}D.$$

Meanwhile, $MV = RR \times VT$, and $\dot{V}D = RR \times VD$, where RR is respiratory rate, $V_T$ is tidal volume, and $V_D$ is dead space volume. Therefore, $\dot{V}A = RR \times V_T - RR \times V_D$, or alternatively, $\dot{V}A = RR(V_T - V_D)$. Then, $Pa_{CO_2} = K \times \dot{V}CO_2/RR(V_T - V_D)$, or

$$Pa_{CO_2} = K \times \dot{V}co_2/RR(1\text{-}V_D/V_T). \qquad (2)$$

Equation 2, a modification of the alveolar ventilation equation, shows the various determinants of steady-state hypercapnia. As an example, the underlying respiratory determinants of hypercapnia in chronic obstructive pulmonary disease (COPD), comparing hypercapnic to eucapnic patients matched for pulmonary function tests, dead space, and $CO_2$ production, are rapid shallow breathing, which results in increased $V_D/V_T$ ratio and $\dot{V}D$ with consequent diminished alveolar ventilation and hypercapnia (9, 10). Importantly, there are no significant differences in global ventilation when the two groups of patients with COPD are compared.

The present study was designed to determine the underlying mechanisms of diurnal hypercapnia in patients with OHS, while exercising extreme care, to the best of our abilities, not to disturb steady state. Frequently, sampling of arterial blood and measuring ventilation are associated with anxiety and other behavioral influences that could disturb steady state. Consequently, the measured $Pa_{CO_2}$ is not accurate. It is for this reason that serum bicarbonate has been suggested as a surrogate (11). The major concern, here, is the potential for "hyperventilation," as the result of which the acid–base disturbance that *in vivo* is chronic respiratory acidosis is interpreted as primary metabolic alkalosis (12), when in reality, the disturbance is post-hypercapnic metabolic alkalosis.

## Methods

### Design

This was a prospective study of 32 consecutive patients. The entry criteria included a history of loud snoring, witnessed apnea, excessive daytime sleepiness, obesity, and other symptoms of OSA syndrome, and a consistent polysomnography (PSG). Most of the patients who participated in this study were part of a larger study in which we measured ventilatory responses of patients and their family members (13). Data were collected from 12 consecutive hypercapnic and 20 eucapnic patients with obstructive sleep apnea–hypopnea syndrome matched for severity of OSA using the metric apnea–hypopnea index (AHI). As noted above, the purpose of this study was not to shed light on the mechanisms of transition from nocturnal hypercapnia to daytime hypercapnia but rather to specifically investigate the respiratory determinants of steady-state hypercapnia while awake.

All patients were male veterans who were referred to the author (S.J.) at a government-based research hospital. For homogeneity, only male patients were included, because female veterans are seldom referred to this center.

### Procedures and Tests

PSG was performed using standard techniques as detailed previously (14, 15). All patients were adapted to the sleep laboratory during the first night by having electrodes placed without recordings being made. PSG was performed during the second night. For staging sleep, we recorded EEG (two channels), chin electromyogram (one channel), and electrooculogram (two channels). Thoracoabdominal excursions were measured qualitatively by respiratory inductance plethysmography (Respitrace; Ambulatory Monitoring Inc., Ardsley, NY) placed over the rib cage and abdomen. Airflow was qualitatively monitored using an oral/nasal thermocouple (Model TCT1R; Grass Instrument Co., Quincy, MA). Arterial blood oxyhemoglobin saturation was recorded using an ear oximeter (Biox IIA; BT Inc., Boulder, CO). These variables were recorded on a multichannel polygraph (Model 78D; Grass Instrument Co., Quincy, MA). An apnea was defined as cessation of inspiratory airflow for 10 seconds or more. An obstructive apnea was defined as the absence of airflow in the presence of rib cage and abdominal excursions. A central apnea was defined as the absence of airflow with absence of rib cage and abdominal excursions. A hypopnea was defined as a discernible reduction of airflow (30%) lasting 10 seconds or more and associated with at least a 4% drop in arterial oxyhemoglobin saturation and/or an arousal (for further details, *see* References 7, 13–15). The number of apneas and hypopneas per hour of sleep is referred to as the AHI. The number of arousals per hour of sleep is referred to as the arousal index.

Coded polysomnograms were scored blindly page by page by one of the authors for staging of sleep, arousals, and respiratory events.

In the morning of PSG, the following tests were obtained: arterial blood gases and pH, ventilation parameters, hypercapnic ventilatory response, and pulmonary function tests. In conducting these tests, extreme caution was exercised to ensure uniformity in technique. Patients were not allowed to drink caffeinated products on the morning of the tests. Tests were performed 2 hours after a meal, and the patients were asked to empty their bladders before the tests. Arterial blood samples were obtained using strict criteria, as detailed previously (13–15). To minimize pain and anxiety, 2% lidocaine was used to anesthetize skin where the radial artery was punctured. Afterward, by touching the patient's skin with a needle, the patient was assured that the procedure was painless. Our hope was to minimize pain and anxiety and, therefore, any attendant change in $Pa_{CO_2}$. With the patient in a sitting position and breathing comfortably for several minutes, an arterial blood sample was obtained painlessly, as attested by the patient. The care used in drawing the blood sample was to assure steady state in the sense that the *in vitro* measured $Pa_{CO_2}$ accurately reflects the *in vivo* value. Details for measurements can be found elsewhere (15).

### Ventilation, $CO_2$ Production, and $O_2$ Consumption

After the arterial blood sampling, ventilation parameters were measured, details of which have been described previously (14, 15). The patients were familiarized with the equipment and breathed through the mouthpiece for several minutes before

measurement began. An assistant monitored the patients continuously to ensure that they remained awake. Ventilation was measured in the sitting position with the subject wearing a nose clip and breathing through a mouthpiece connected to a low-resistance two-way valve (Hans-Rudolph, Kansas City, MO). Measurements were started several minutes after a stable baseline had been achieved (i.e., stable end-tidal $P_{CO_2}$ for several minutes).

Airflow and the volume were measured by a pneumoscan (S-301; KL Engineering Co., Sylmar, CA). Calibrations were performed by known flow rates from pneumatic calibrator (model 65–250; Penwalt, Cor, Belleville, NJ) and for volume by a 3-L syringe. End-tidal $CO_2$ was sampled at the mouthpiece by an infrared $CO_2$ analyzer (Beckman medical gas analyzer, LB-2; Beckman Cardiopulmonary Instruments, Fullerton, CA), which was calibrated with gases of known $CO_2$ concentrations.

Resting ventilation was measured as the subject breathed room air for 3 minutes while exhaled gas was collected for measurement of mixed expired $CO_2$ and $O_2$ concentrations by gas analyzer. Dead space was calculated using the Bohr equation, the known arterial, and the mixed-expired $P_{CO_2}$. Alveolar ventilation was calculated by subtracting $\dot{V}_E$ (the product of $V_T$ times breathing rate) from dead space ventilation (the product of $V_D$ times breathing rate). Respiratory quotient was calculated as the ratio of $CO_2$ production over oxygen consumption.

### Hypercapnic Ventilatory Response

The hypercapnic ventilatory response (HCVR) was measured in the sitting position with the subject wearing a nose clip and breathing through a mouthpiece connected to a low-resistance two-way valve. Details of the test as performed in our laboratory have been previously described (7, 14, 15). Measurements were started several minutes after a stable baseline had been achieved (i.e., ventilation and end-tidal $P_{CO_2}$ had not changed for several minutes). The hyperoxic HCVR was determined by Read's rebreathing method. Linear regression was used to determine the slope according to the equation: $\dot{V} = S \times Pa_{CO_2} - B$, where S is the slope of HCVR and B is the intercept (on the abscissa) of the line that relates ventilation to $P_{CO_2}$.

### Pulmonary Function Tests

For measurements of lung volume, flow rates, and single breath carbon monoxide diffusing capacity, we used an automated system (Collings/DS560; Braintree, MA) as detailed previously (16). Maximum voluntary ventilation was measured by instructing the subject to breathe as quickly and as deeply as possible for 12 seconds. For further reference, these procedures have been described previously (7).

Left and right ventricular ejection fractions were also measured by radioactive technique as reported previously (17), either the day before or after PSG.

The protocol was approved by the Institutional Review Board of the University of Cincinnati College of Medicine. All patients signed informed consent.

### Statistical Analysis

Unpaired two-tailed *t* tests were used to determine differences of statistical significance between the two groups. Data are presented as means ± SD, and *P* less than 0.05 was considered significant. Dichotomous categorical values were compared using Chi-square tests. Calculations were performed using SAS 9.0.

## Results

Hypercapnic patients were significantly heavier with a greater body mass index than eucapnic patients (Table 1). Hypercapnic patients, as expected, had a lower $FEV_1$ and FVC than eucapnic patients; however, the mean values of the percent predicted $FEV_1$/FVC ratio were normal and did not differ significantly between the two groups.

There were no significant differences in left (48%, n = 12 vs. 54%, n = 15) or right (48%, n = 12 vs. 49%, n = 15) ventricular ejection fractions between and hypercapnic and eucapnic patients (15 of the 20 patients).

As expected, hypercapnic patients also had significantly greater plasma $[HCO_3^-]$ than eucapnic patients, reflecting the chronicity of $CO_2$ retention (Table 2). The mean value of the hypercapnic ventilatory response was significantly lower in the hypercapnic than in the eucapnic patients. Also in part imposed by hypercapnia, the mean $Pa_{O_2}$ was significantly lower in hypercapnic patients.

There were no significant differences in ventilation parameters, and the mean values of $V_E$ and alveolar ventilations were similar between the two groups. Hypercapnic patients had a significantly greater $CO_2$ production ($P = 0.02$) and trended toward higher oxygen consumption ($P = 0.06$) than eucapnic patients; importantly, when these values were adjusted for body surface area, there were no significant differences between the two groups. Respiratory quotients were within normal range and did not differ significantly between the two groups. The normal values for respiratory

**Table 1.** Anthropomorphic and pulmonary function tests of hypercapnic and eucapnic patients with sleep apnea–hypopnea syndrome

| | Hypercapnic (*n* = 12) | Eucapnic (*n* = 20) | *P* Value |
|---|---|---|---|
| Age, yr | 51 ± 11 | 53 ± 9 | 0.68 |
| Weight, kg | 159 ± 23 | 121 ± 22 | 0.0001 |
| Height, cm | 180 ± 8 | 176 ± 4 | 0.04 |
| Body mass index, kg/m$^2$ | 49 ± 8 | 39 ± 6 | 0.0004 |
| Body surface area, m$^2$ | 2.66 ± 0.21 | 2.34 ± 0.20 | 0.0002 |
| $FEV_1$, L/s | 2.34 ± 0.85 (61 ± 19) | 2.98 ± 0.82 (84 ± 21) | 0.04 (0.004) |
| FVC, L | 2.93 ± 0.10 (63 ± 19) | 3.77 ± 1.04 (87 ± 21) | 0.03 (0.003) |
| $FEV_1$/FVC, % | 79 ± 6 (97 ± 6) | 79 ± 5 (97 ± 7) | 0.91 (0.96) |
| FRC, L | 2.31 ± 0.58 | 2.40 ± 0.64 | 0.69 |
| TLC, L | 5.06 ± 0.95 (75 ± 15) | 5.73 ± 1.06 (90 ± 16) | 0.09 (0.014) |
| RV, L | 2.06 ± 0.66 (65 ± 19) | 1.86 ± 0.04 (94 ± 21) | 0.03 (0.0004) |
| Diffusing capacity for CO, ml/min/mm Hg | 27 ± 8 (93 ± 28) | 28 ± 8 (97 ± 28) | 0.86 (0.69) |
| Maximum voluntary ventilation, L/min | 93 ± 37 (58 ± 20) | 118 ± 36 (87 ± 32) | 0.07 (0.007) |
| Slope of HCVR, ml/min/mm Hg | 1.39 ± 0.57 | 2.83 ± 2.31 | 0.04 |

*Definition of abbreviations*: HCVR = hypercapnic ventilatory response; RV = residual volume. Values are mean ± SD. Values in parenthesis are percent predicted.

**Table 2.** Ventilation data of hypercapnic and eucapnic patients with sleep apnea–hypopnea syndrome

| | Hypercapnic (*n* = 12) | Eucapnic (*n* = 20) | *P* Value |
|---|---|---|---|
| $Pa_{CO_2}$, mm Hg | 52 ± 5 | 40 ± 3 | 0.0001 |
| $Pa_{O_2}$, mm Hg | 59 ± 8 | 75 ± 10 | 0.0001 |
| $[H^+]$, nEq/L | 40 ± 4 | 39 ± 2 | 0.39 |
| $[HCO_3^-]$, mEq/L | 32 ± 4 | 25 ± 2 | 0.0001 |
| Breathing rate, n/min | 14.9 ± 3.9 | 14.0 ± 4.4 | 0.59 |
| $V_T$, ml | 834 ± 124 | 853 ± 208 | 0.78 |
| $\dot{V}_E$, L/min | 12.2 ± 3.0 | 11.6 ± 2.0 | 0.52 |
| $\dot{V}_E$/BSA, L/min/m$^2$ | 4.6 ± 1.0 | 5.0 ± 0.09 | 0.26 |
| Alveolar ventilation, L/min | 5.7 ± 1.5 | 6.1 ± 1.5 | 0.53 |
| Alveolar ventilation/BSA, L/min/m$^2$ | 2.2 ± 0.5 | 2.6 ± 0.6 | 0.04 |
| Dead space, ml | 436 ± 59 | 397 ± 8 | 0.18 |
| Dead space ventilation, L/min | 6.5 ± 2.0 | 5.5 ± 1.6 | 0.13 |
| Dead space ventilation/BSA, L/min/m$^2$ | 2.4 ± 0.7 | 2.4 ± 0.7 | 0.82 |
| Dead space/$V_T$ ratio, % | 53 ± 7 | 48 ± 9 | 0.10 |
| $CO_2$ production, ml/min | 336 ± 79 | 278 ± 58 | 0.02 |
| $CO_2$ production/BSA, ml/min/m$^2$ | 126 ± 27 | 119 ± 22 | 0.40 |
| Oxygen consumption, ml/min | 435 ± 101 | 360 ± 89 | 0.06 |
| Oxygen consumption/BSA, ml/min/m$^2$ | 164 ± 34 | 153 ± 36 | 0.40 |
| Respiratory quotient | 0.80 ± 0.10 | 0.82 ± 0.13 | 0.60 |

*Definition of abbreviation*: BSA = Body surface area.
Values are mean ± SD. All ventilation data are in body temperature pressure saturated except for $CO_2$ production and $O_2$ consumption, which are in standard temperature pressure saturated.

quotients are consistent with steady-state conditions critical to our measurements.

Polysomnographic data are presented in Table 3. There were no significant differences in mean values for sleep efficiency, sleep onset, percent REM and non-REM sleep, or AHI (the matching variable) when hypercapnic and eucapnic patients were compared. The major difference was related to desaturation (Table 3).

## Discussion

The important findings of the current study are: (*1*) Patients with OHS have an increased baseline metabolic rate, which is characterized by increased carbon dioxide production and oxygen consumption. (*2*) When the parameters of metabolic rate are adjusted for body surface area, the differences between hypercapnic and eucapnic patients become statistically nonsignificant. (*3*) In this group of patients with OHS, carbon dioxide hyperproduction was the main reason for chronic $CO_2$ retention, as the mean values for $\dot{V}_E$ and $\dot{V}_A$ were similar when compared with eucapnic patients.

Patients with OHS, by definition, have elevated daytime $Pa_{CO_2}$. The mechanisms that result in spillover from nocturnal hypercapnia to daytime hypercapnia have been speculated (7) and studied in detail by Berger and colleagues (18–20), Norman and colleagues (21), and Ayappa and colleagues (22). To our knowledge, our study is the first exploring the physiological respiratory mechanisms of diurnal hypercapnia. We had hypothesized that patients with OHS have lower $\dot{V}_E$ and $\dot{V}_A$ than eucapnic patients. To our surprise, this was not the case, and the major mechanism for hypercapnia was $CO_2$ hyperproduction.

**Table 3.** Polysomnographic data of hypercapnic and eucapnic patients with sleep apnea–hypopnea syndrome

| | Hypercapnic (*n* = 12) | Eucapnic (*n* = 20) | *P* Value |
|---|---|---|---|
| Total recording time, min | 336 ± 88 | 322 ± 64 | 0.60 |
| Total sleep time, min | 249 ± 95 | 250 ± 60 | 1.0 |
| Sleep efficiency, % | 70 ± 20 | 80 ± 12 | 0.09 |
| Sleep onset, min | 10 ± 15 | 12 ± 18 | 0.80 |
| Non-REM/total sleep time, % | 85 ± 8 | 88 ± 10 | 0.40 |
| REM/total sleep time, % | 15 ± 8 | 11 ± 8 | 0.17 |
| Apnea–hypopnea index, n/h | 50 ± 33 | 47 ± 33 | 0.80 |
| Baseline saturation, % | 92 ± 3 | 95 ± 2 | 0.003 |
| Lowest saturation, % | 55 ± 17 | 65 ± 13 | 0.05 |

The major function of the respiratory system is to maintain partial pressures of arterial blood oxygen and carbon dioxide and pH normal. Normally, steady-state $Pa_{CO_2}$ is tightly regulated via a negative feedback system. This homeostatic regulation is achieved by adjustment of ventilation to the metabolic carbon dioxide production (Equation 1). In this way, $Pa_{CO_2}$ is tightly controlled and remains constant throughout life (8).

Pathophysiologically, there are four respiratory mechanisms that can result in daytime hypercapnia (8, 23). These include (*1*) decreased global and alveolar ventilation, as occurs with use of respiratory depressant medications such as opioids, a condition wherein the use of the term hypoventilation is most appropriate; (*2*) ventilation/perfusion mismatch impairing $CO_2$ clearance (23) unless ventilation rises enough to increase alveolar ventilation to compensate for ventilation/perfusion mismatch as it commonly occurs in interstitial lung diseases (24); (*3*) a pattern of breathing characterized by diminished $V_T$ and increased breathing rate as it occurs in hypercapnic patients with COPD (9, 10), the so-called blue bloaters; and (*4*) increased $CO_2$ production not compensated by increased $\dot{V}_E$ and alveolar ventilation as it occurred in our patients.

As noted above, normally there is coupling of carbon dioxide production with alveolar ventilation, such that $Pa_{CO_2}$ remains constant. A relevant example is exercise, where in spite of several-fold increase in $CO_2$ production, $Pa_{CO_2}$ remains constant (as long as anaerobic threshold is not reached). Therefore, based on the results of the present study, in patients with OHS, there is uncoupling between $CO_2$ production, which is increased, and lack of compensation by the respiratory system. Now that this uncoupling has been demonstrated, the question is if this is due to a "cannot breathe" or "do not want to

breathe" mechanism, or the combination of the two? This study was not designed to answer this question, and the discussion of evolution of diurnal hypercapnia is beyond the scope of this manuscript. However, we suggest that decreased ventilatory response could be the consequence rather than the cause of $CO_2$ retention (7, 25). The massive obesity imposes both mechanical impairment (poor chest wall compliance, curtailing maximum ventilation when needed, for example, in response to an apnea) and increased $CO_2$ load (respiratory and nonrespiratory production). These are critical factors that impair $CO_2$ clearance during interapneic periods when ventilation needs to increase to unload the huge amount of metabolically produced $CO_2$ and retained during obstructive apneic periods. It is hypothesized that with prolonged nocturnal $CO_2$ retention, plasma $HCO_3^-$ concentration gradually rises (7, 19, 25), decreasing ventilatory response to $CO_2$ (12). However, it is certainly plausible that a diminished ventilatory response could predispose to chronic daytime hypercapnia, although we emphasize that diminished hypercapnic ventilatory response in patients with OHS does not appear to have a genetic predisposition (13). On the other hand, a diminished ventilatory response to $CO_2$ could contribute to maintenance of diurnal hypercapnia.

Studies in the literature suggest respiratory muscle fatigue and impaired endurance (for reviews, *see* References 1–3, 5, 6). In the present study, maximum voluntary ventilation was trending lower in patients with OHS compared with eucapnic patients. Considering that the test was only 12 seconds in duration and with small number of patients, our data are potentially consistent with the fatigue paradigm.

We should note that a number of studies are available showing that weight loss (26, 27), as well as treatment with positive airway pressure devices (28–33), improves $Pa_{CO_2}$, although residual hypercapnia may persist in spite of excellent adherence to positive airway pressure therapy (31). So far, the results of such studies have been interpreted as if the improvement in sleep apnea was the only mechanism by which $Pa_{CO_2}$ improved. The results of the current study shed light on an additional and important mechanism contributing to the normalization of $Pa_{CO_2}$. Furthermore, residual hypercapnia after treatment with positive airway pressure devices may be due to persistent $CO_2$ hyperproduction of obesity.

In fact, comparing the collective information of both groups, the polysomnographic (matched AHI values, Table 2) and ventilation data (Table 3) suggest that weight loss by itself, even in the absence of any improvement in AHI, could potentially convert the phenotype of OSA from hypercapnic to eucapnic. We emphasize, however, the small number of patients enrolled, which could have affected our findings.

In the present study, there were no significant differences in $\dot{V}_E$ between the two groups, as noted earlier. These results appear to be somewhat similar to the study of Pankow and colleagues (34). These authors measured supine $\dot{V}_E$ in six patients with OHS, seven eucapnic patients with OSA, and five obese participants. Comparing the first two groups, respective values for $\dot{V}_E$ were 10 and 8.4 L/min (*P* value not reported). Authors did not measure $CO_2$ production; however, respective mean values for body mass indices were 44 and 46 $kg/m^2$. This difference in body weight, resulting in excess $CO_2$ production in patients with OHS, perhaps along with lower $\dot{V}_E$, could have accounted for hypercapnia. We emphasize the small number of patients and differences in design, which include use of face mask, insertion of an esophageal balloon, and supine measurements. Regarding increased $CO_2$ production and increased $O_2$ consumption associated with obesity, our results confirm those of previous studies (35, 36).

### Clinical Implications

When compared with patients with OSA and normal $Pa_{CO_2}$, patients with OSA and hypoventilation have decreased quality of life, excess healthcare cost, increased morbidity, and premature mortality (37, 38). These adverse consequences are not the result of high $Pa_{CO_2}$ adversely affecting enzymatic function by acidemia, because with renal compensation, pH is normalized (Table 2). However, based on Dalton's law, a high $Pa_{CO_2}$ imposes a low $Pa_{O_2}$ (Table 2), and hypoxemia results in a number of adverse consequences, including activation of redox-sensitive genes with consequent production of reactive oxygen species and activation of an inflammatory cascade (39). Yet, we should emphasize that administration of supplemental oxygen could be associated with worsening hypercapnia (40).

An important implication of our data is that excess $CO_2$ production is directly related to body surface area. Thus, weight loss should have a major impact on metabolic production of $CO_2$ (and consumption of oxygen) with a decrease in $Pa_{CO_2}$ and, based on Dalton's law, an incremental increase in $Pa_{O_2}$. Normalization of oxygen balance is critical in prevention of organ dysfunction due to hypoxia.

### Summary

Patients with OSA and OHS, when matched with eucapnic patients with OSA, are more obese, have much higher $CO_2$ production, but have similar $\dot{V}_E$ and alveolar ventilation. Therefore, $CO_2$ hyperproduction accounts for their hypercapnia. And when $CO_2$ production is adjusted for body surface area, there is no significant difference between hypercapnic and eucapnic patients. In part due to hypercapnia, patients with OHS have hypoxemia, which should contribute to activation of inflammatory pathways and organ dysfunction. Our data suggest that weight loss *per se* could change the hypercapnic OSA to eucapnic phenotype and simultaneously improve oxygenation. Improved oxygen balance should minimize long-term organ damage associated with OHS. ■

**Author disclosures** are available with the text of this article at www.atsjournals.org.

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