Hypercapnic Ventilatory Response in Patients With and Without Obstructive Sleep Apnea*

Do Age, Gender, Obesity, and Daytime Paco2 Matter?

Don D. Sin, MD, MPH; Richard L. Jones, PhD, FCCP; and Godfrey C. Man, MB BS, FCCP

Study objective: To evaluate the relationship between obstructive sleep apnea (OSA) and ventilatory responsiveness to carbon dioxide in both men and women.

Design: An analysis of 219 patients referred to an university-based sleep center between 1989 to 1994 was conducted (104 with OSA and 115 without OSA; 43 women and 176 men). These patients had spirometry and a daytime hypercapnic ventilatory response (HCVR) test that was corrected to the patient’s ability to attain maximal ventilation. Comparisons between OSA and no-OSA groups, as well as between men and women, were made using multivariate modeling techniques.

Results: There was no significant difference in the slope of correlated HCVR (cHCVR) between those with and without OSA (1.57 ± 0.57 vs 1.63 ± 0.66; p = 0.48). In men, an inverse correlation between daytime PCO2 and cHCVR was observed in both crude and multivariate analyses (crude β-coefficient = −0.04 ± 0.02, p = 0.02; adjusted β-coefficient = 0.07 ± 0.02, p < 0.01). Although age and cHCVR did not share a significant relationship in the crude analysis (crude β-coefficient = −0.01 ± 0.01, p = 0.10), with adjustments for confounding variables, a significant inverse relationship between age and cHCVR was observed (β-coefficient = −0.02 ± 0.01, p = 0.04). On the other hand, in women, only body mass index (BMI) was positively correlated with cHCVR (crude β-coefficient = 0.03 ± 0.01, p = 0.01; adjusted β-coefficient = 0.04 ± 0.01, p < 0.01).

Conclusion: OSA disorder is not associated with a blunted ventilatory chemoresponsiveness to carbon dioxide. Elevated PaCO2 and older age are significant correlates for a low cHCVR in men. For women only, BMI was associated with cHCVR. These findings suggest that men and women may have different ventilatory control mechanisms.

Key words: carbon dioxide; control of breathing; gender; obesity; obstructive sleep apnea

Abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; cHCVR = correlated hypercapnic ventilatory response; CI = confidence interval; HCVR = hypercapnic ventilatory response; nCPAP = nasal continuous positive airway pressure; OSA = obstructive sleep apnea; Ve = minute ventilation; %Ve max = percent of predicted Ve.

Obstructive sleep apnea (OSA) is a common disorder in the community. Some patients with OSA have a blunted ventilatory response to chemical stimulation, which may be reversed with the elimination of nocturnal apneic events by either tracheostomy or nasal continuous positive airway pressure (nCPAP). Diminished chemosensitivity of ventilatory response in untreated OSA may predispose these patients to chronic hypercapnic respiratory failure and cor pulmonale. On the other hand, others have suggested that OSA patients have a heightened responsiveness to hypercapnia, which may contribute to respiratory control instability and upper airway obstruction. Studies that have evaluated the relationship between ventilatory responsiveness to hypercapnia and OSA have shown inconsistent results. Verbraecken et al., for instance, observed an increase in response to hypercapnia in 14 normocapnic OSA patients. Garay et al., in contrast, showed normal responses to hypercapnic stimulation in six eucapnic OSA patients. In both studies, hypercapnic OSA patients demonstrated a blunted response to hypercapnia. Lopata and Onal reported a diminished response to hypercapnia in 15

*From the Department of Medicine, Division of Respirology, University of Alberta, Edmonton, Alberta, Canada. Dr. Sin is supported by a fellowship from the Alberta Heritage Foundation for Medical Research. Manuscript received September 4, 1998; revision accepted September 8, 1999.

Correspondence to: Godfrey C. Man, MB BS, FCCP, 2E4.44 Walter C. Mackenzie Centre, University of Alberta Edmonton, Alberta, Canada; e-mail: mang@ualberta.ca
OSA patients, half of whom were normocapnic. Several studies have shown that treatment with either tracheostomy or nCPAP can reverse diminished ventilatory responsiveness in some, but not in all patients.\textsuperscript{4,5} Inadequate control of confounding variables, such as obesity, age, gender, and presence of concomitant conditions make interpretation of these studies difficult. Moreover, these studies have enrolled relatively few patients, resulting in diminished statistical power. In addition, most of the subjects to date have been men and the influence of gender on ventilatory responsiveness in OSA has not been adequately evaluated. Therefore, we studied a large group of patients with and without OSA to ascertain the independent effects of OSA on hypercapnic ventilatory response (HCVR), to identify important determinants of HCVR, and to explore gender differences in ventilatory response, since previous studies in healthy subjects have suggested that regulation of ventilation is governed by different factors between men and women.\textsuperscript{10,11} Specifically, we tested the hypotheses that age, gender, OSA, and obesity would be significantly correlated with HCVR.

**MATERIALS AND METHODS**

We reviewed the files of 249 consecutive patients (seen by G.C.M.) who underwent nocturnal polysomnography for suspicion of OSA at the University of Alberta Sleep Center between 1989 and 1994. As part of their workup, all of these patients underwent a daytime HCVR test. In view of the possible interactions between hypnotics and major tranquilizers on ventilatory responsiveness, we excluded 24 patients who were actively taking these medications at the time of their assessment in our clinic. We also excluded one patient who had central sleep apnea and five patients who had technically unacceptable HCVR results. The exclusion of these patients reduced our sample size to 219 subjects.

Nighttime polysomnography was performed using standard polysomnographic techniques, and sleep was staged according to standard criteria.\textsuperscript{12} Nocturnal polysomnography consisted of EEG, electro-ocularogram, submental electromyogram, recordings of nasal airflow by thermistor, respiratory effort by inductance plethysmography, ECG, leg movements by leg electrodes, and oxygen saturation by finger oximeter. Obstructive apneas were defined by paradoxical motion of rib cage and abdomen, in the absence of airflow for at least 10 s. Obstructive hypopneas were defined as a \( \geq 50\% \) reduction in airflow with abdominal and chest wall motions consistent with obstructive events, persisting for at least 10 s. To allow comparability with other reported studies, we decided a \textit{priori} to use an apnea-hypopnea index (AHI) of 15 to dichotomize between those with sleep apnea from those without. Using this criteria, 104 patients had OSA and 115 without, and compared baseline characteristics as well as HCVR.

We initially classified patients as those with OSA and those without, and compared baseline characteristics as well as HCVR. To determine whether or not OSA was an independent correlate of HCVR, we used a multivariate regression analysis, adjusting for important covariates, which included gender, age, and body mass index (BMI). In the secondary analysis, the patient population was divided into men and women. Comparisons of baseline characteristics as well as HCVR were also made between these two groups, and similar statistical methods were used to identify significant correlates of HCVR in both men and women.

Data were analyzed with SAS software modules (Version 6.10; SAS Institute; Cary, NC) for descriptive statistics and multiple regression analyses. Two-tailed \( p \) values \(< 0.05\) were considered to indicate statistical significance. BMI was calculated using the standard formula: weight (in kilograms) divided by height (meters squared). Two-way interactions of BMI, gender, \( P_{\text{aCO}_2} \), age, and AHI were examined. All data are presented with mean \( \pm \) SD unless otherwise indicated.

**RESULTS**

Baseline features of subjects with and without OSA are presented in Table 1. OSA was associated with higher BMIs and a higher prevalence of female subjects. Extreme obesity (BMI > 40), however, was uncommon in either group; but among those who

| Variables          | OSA (n = 104) | No OSA (n = 115) | \( p \)  \\
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<tbody>
<tr>
<td>Age, yr</td>
<td>47.7 ( \pm ) 10.7</td>
<td>45.4 ( \pm ) 11.5</td>
<td>0.13</td>
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<tr>
<td>Female gender, %</td>
<td>7</td>
<td>30</td>
<td>&lt; 0.01</td>
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<tr>
<td>BMI, kg/m(^2)</td>
<td>31.4 ( \pm ) 6.2</td>
<td>29.6 ( \pm ) 5.9</td>
<td>0.03</td>
<td></td>
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<tr>
<td>( P_{\text{aCO}_2} ), mm Hg</td>
<td>37.4 ( \pm ) 3.0</td>
<td>37.2 ( \pm ) 2.6</td>
<td>0.65</td>
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<tr>
<td>AHI</td>
<td>42.6 ( \pm ) 24.5</td>
<td>5.9 ( \pm ) 4.3</td>
<td>&lt; 0.01</td>
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<tr>
<td>HCVR, L/min/mm Hg</td>
<td>1.93 ( \pm ) 0.81</td>
<td>1.79 ( \pm ) 0.75</td>
<td>0.18</td>
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<tr>
<td>( c\text{HCVR}, % V_{\text{Emax}}/\text{mm Hg} )</td>
<td>1.63 ( \pm ) 0.66</td>
<td>1.57 ( \pm ) 0.57</td>
<td>0.48</td>
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*Data are presented as mean \( \pm \) SD, unless otherwise indicated.
had BMI > 40, 7 of the 20 (35%) had OSA by our a priori criteria. Correlates for cHCVR were determined using a linear regression modeling technique, and the results are shown in Table 2. PaCO₂ was inversely associated with cHCVR, such that a 1-mm Hg increase in PaCO₂ was associated with 0.031 decrease in cHCVR (95% confidence interval [CI], 0.002 to 0.060; p = 0.037). BMI, on the other hand, shared a positive linear relationship with cHCVR. For the whole group, a 10-U increase in BMI resulted in a 0.19-U increase in cHCVR (95% CI, 0.05 to 0.3; p = 0.006). When BMI was evaluated as a categorical variable using the BMI cutoff points specified above, patients who had normal or near-normal BMI had the lowest cHCVR, whereas those who were most overweight had the highest mean cHCVR. However, the magnitude of change was greatest between those with BMI < 28.1 kg/m² and those with BMI from 28.1 to 30.0 kg/m², suggesting a possible threshold effect of BMI on cHCVR. All other variables including AHI, age, gender, and a diagnosis of OSA were not significantly associated with cHCVR. In the initial analysis, OSA was weakly associated with cHCVR (β-coefficient = 0.170 ± 0.104; p = 0.10). However, in the adjusted analysis, the β-coefficient was reduced to 0.061 (p = 0.40), indicating no significant association between OSA and HCVR.

Twenty percent of our study patients were women; of these, only 7 of 43 (16%) had an AHI ≥ 15. In contrast, 96 of 176 men (55%) had an AHI ≥ 15. Among patients with extreme obesity (BMI > 40 kg/m²), the prevalence of OSA was similar between men and women (11 of 15 vs 3 of 5, respectively). However, the mean AHI of this group was much lower in women than in men (11 vs 47, respectively). When each of the gender groups was dichotomized into those with OSA from those without, women with OSA were older than women without OSA (53 years vs 31 years). However, no such age difference could be found in men (46 years vs 48 years), suggesting that while age is not a risk factor for OSA in men, age appears to be an important correlate of OSA in women. Table 3 shows gender differences in the measured variables. The mean HCVR was lower in women than men. However, the corrected HCVRs were similar, indicating that as a group, women had lower FEV₁ values than men, which accounted for the differences in the uncorrected HCVR results.

Correlates for an abnormally low cHCVR were different between men and women. In men, age and daytime arterial PaCO₂ (Fig 1) shared a significant inverse relationship with cHCVR. Increasing age was associated with a decrease in cHCVR, such that a 10-year increment in age was associated with a 0.2-U decrease in cHCVR (p = 0.04). In men, a 10-mm Hg increment in PaCO₂ was associated with a 0.7-U decrease in cHCVR (p < 0.001). However, in men there was no significant correlation between BMI and cHCVR (crude β-coefficient = 0.01 ± 0.01, p = 0.108; adjusted β-coefficient = 0.01 ± 0.01, p = 0.094), or between BMI and HCVR (β-coefficient = 0.004 ± 0.01, p = 0.725; Fig 2).

<table>
<thead>
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<th>Table 2—Correlates for cHCVR in all Patients</th>
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<tr>
<td>Variables</td>
</tr>
<tr>
<td>Age</td>
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<tr>
<td>Male gender</td>
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<td>BMI</td>
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<td>PaCO₂</td>
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<th>Table 3—Baseline Characteristics of Male and Female Subjects</th>
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<td>Variables</td>
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<tr>
<td>Age, yr</td>
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<tr>
<td>BMI, kg/m²</td>
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<tr>
<td>PaCO₂, mm Hg</td>
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<td>AHI</td>
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<td>HCVR, L/min/mm Hg</td>
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<td>cHCVR, %V˙ₑmax/mm Hg</td>
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FIGURE 1. The effect of daytime PaCO₂ on cHCVR in men and women. Dashed lines represent 95% CI in women. Slashed lines represent 95% CI in men. δ p = < 0.001; %Vₑmax.
On the other hand, for women, only BMI shared a significant relationship with cHCVR. A 10-U increment in BMI was associated with 0.04-U increase in cHCVR in women ($p = 0.002$).

**FIGURE 2.** The effect of BMI on chCVR in men and women. Dashed lines represent 95% CI in women. $\delta p = 0.002$.

**DISCUSSION**

We have found that OSA is not independently associated with cHCVR or daytime PaCO$_2$. Our results appear to conflict with other studies that have shown an inverse relationship between AHI and HCVR. Since many factors influence HCVR, confounding by other variables is an important threat to the validity of results. Airways obstruction, for instance, has been shown to be an independent correlate of daytime hypercapnia among OSA patients. Since obstructive airways disease is common in the obese, failure to take into account the patients’ reduced ability to breathe could lead to an underestimation of their HCVR. We have addressed this issue by using a modified HCVR equation, which takes into account the patient’s predicted maximal ventilation as well as using multiple regression techniques to control for underlying comorbid pulmonary conditions that could also influence HCVR. Indeed, in the baseline analysis, OSA was weakly associated with HCVR ($\beta$-coefficient = 0.170 ± 0.104, $p = 0.10$). However, with adjustments for age, gender, BMI, and FEV$_1$, $\beta$-coefficient was reduced to 0.061 ($p = 0.46$), suggesting that OSA was not related to HCVR and that there was considerable confounding by these variables.

Our findings indicate that there are clear gender differences in the factors affecting chCVR. In men, the main determinants of abnormal chCVR were daytime hypercapnia and, to a lesser extent, age. The negative association between daytime PaCO$_2$ and HCVR is well established. The causality of the relationship, however, is unclear. Primary disorders of the central chemoreceptors can produce hypoventilation and elevations in daytime PaCO$_2$, as in pickwickian syndrome. On the other hand, chronic exposure to hypercapnia or hypoxia from diffuse airways disease or other disease processes could reset the ventilatory threshold and/or alter ventilatory responsiveness, changing the position or the slope of the HCVR curve, respectively. Regardless of the cause, a low HCVR is a risk factor for the development of hypercapnic respiratory failure. Given the relationship between arterial PCO$_2$ and HCVR, arterial blood gases may be useful to identify patients at high risk for developing hypercapnic respiratory failure.

Our findings also indicate that the aging effect on ventilatory responsiveness, when adjusted for lung function, is quite modest. This observation is consistent with previous findings that have demonstrated that aging process per se has little or no impact on ventilatory responsiveness, unless complicated by disease conditions or medications.

Unlike men, in women, daytime PaCO$_2$ did not correlate with cHCVR. BMI was the only significant correlate for cHCVR. The association between weight and cHCVR is controversial. Lopata and Onal have shown that mass loading of the chest wall blunts ventilatory responsiveness, suggesting that obesity could in certain cases lead to hypoventilation. Conversely, Chapman et al have described a positive association between BMI and HCVR in obese subjects undergoing gastroplasty. The discrepancy in results may be due to the differences in weight distribution of the upper abdomen. With natural weight gains, adiposity is distributed circumferentially around the abdomen. On the other hand, under experimental conditions, weights are preferentially placed on the upper abdomen, which is likely to place a greater burden on the respiratory system than that with natural obesity. Hence, such experiments may mimic conditions arising from severe obesity, but is unlikely to reflect those of mild to moderate obesity, which frequently occurs in OSA. Chapman et al have demonstrated that HCVR decreases with weight reduction, following gastroplasty, in the absence of a concomitant change in lung function. While the mechanism is not entirely clear, previous studies have shown that obese individuals have a higher metabolic rate than lean patients, which may augment respiratory drive and HCVR. In addition, since some fat stores are peripherally converted to estrone and other estrogen products, obesity may increase the slope of HCVR through this mechanism. In female patients, the latter mechanism is more likely to be operative, as previous studies have shown that women have a blunted ventilatory response to metabolic stimulants.
including hyperthermia and mild exercise, \textsuperscript{28} and an augmented ventilatory response to progesterone and, to a lesser extent, estrogen. \textsuperscript{10} This suggests that the central control of ventilation in women is preferentially under hormonal regulation and is less influenced by chemical and metabolic factors. Our study demonstrates that, in women, BMI but not daytime PaCO\textsubscript{2} correlates with HCVR, which supports this notion.

Unlike previous studies, we used an HCVR value that was corrected for the patients’ ability to breathe. We have shown previously that lung function, as measured by FEV\textsubscript{1}, correlates significantly with HCVR, whereas occlusion pressure response to hyperventilation and cHCVR does not. \textsuperscript{14,15} Therefore, without adjustment for FEV\textsubscript{1}, the relationship between chemoresponsiveness and hyperventilation may be confounded by impairments in lung or chest wall mechanics. Moreover, HCVR does not correlate well with arterial P\textsubscript{CO}\textsubscript{2}. In contrast, there is a significant inverse association between cHCVR and arterial P\textsubscript{CO}\textsubscript{2}, providing further evidence that cHCVR is the more appropriate measure of chemoresponsiveness. \textsuperscript{14}

Several limitations should be addressed. First, we used patients who were referred to a sleep laboratory without sleep apnea as our control subjects. These patients are likely to have a more disrupted sleep architecture than normal control subjects in the community. However, Espinoza et al. \textsuperscript{29} have shown that sleep fragmentation alone is unlikely to change HCVR in those without sleep apnea. Second, our study was cross-sectional in nature. Because we could not estimate the burden of OSA for each individual patient, we cannot rule out the possibility that a prolonged exposure to obstructive apneas and hypopneas may, in some cases, diminish chemosensitivity. However, previous studies have demonstrated efficacy in restoring ventilatory responsiveness with nCPAP or tracheostomy in patients with severe OSA, \textsuperscript{4,5} suggesting that length of disease is unlikely to be an important determinant. Third, in the present study, we had few extremely obese patients (BMI > 40 kg/m\textsuperscript{2}) or patients who manifested significant daytime hypoventilation (PaCO\textsubscript{2} > 45 mm Hg). Berthon-Jones and Sullivan \textsuperscript{5} have shown that only those OSA patients with significant daytime hypoventilation demonstrate an abnormal HCVR, which reverses with nCPAP treatment. However, because their group of patients tended to be morbidly obese, the effect of adiposity on the respiratory system may have confounded their results. In the present study, we have found no significant association between AHI and daytime PaCO\textsubscript{2}, arguing against nocturnal obstructive events playing an important role in the reduction of chemosensitivity to hypercapnia. However, because only a small number of our patients had daytime hypercapnia, we cannot confidently rule out a possible contributory role of apneic events in these patients.

In summary, although previous experiments have shown that OSA may depress ventilatory chemoresponsiveness, \textsuperscript{7} our data indicate that there is no significant association between AHI and cHCVR, suggesting that intermittent exposures to apneic events are insufficient to reset the ventilatory thermostat. In men, primary determinants of cHCVR in both patients with and without OSA are age and daytime PaCO\textsubscript{2}; in women, BMI appears to be the more significant factor. Our findings are consistent with the concept that ventilatory control in women is predominantly regulated by hormonal mechanisms; in men, chemical or metabolic factors have a more prominent role in ventilatory regulation.


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