Human Obesity Is Characterized by a Selective Potentiation of Central Chemoreflex Sensitivity

Krzysztof Narkiewicz, Masahiko Kato, Catherine A. Pesek, Virend K. Somers

Abstract—The chemoreflexes are an important mechanism for regulation of both breathing and autonomic cardiovascular function. Obesity is associated with an increased risk of alveolar hypoventilation and carbon dioxide retention, suggesting that abnormalities in chemoreflex control mechanisms may be implicated. We tested the hypothesis that chemoreflex function is altered in obesity. We compared ventilatory, sympathetic, heart rate, and blood pressure responses to hypercapnia, hypoxia, and the cold pressor test in 14 obese subjects and 14 normal-weight subjects matched for age and gender. During hypercapnia, the increase in minute ventilation was significantly greater in obese subjects (7.0±0.3 L/min) than in normal-weight subjects (3.3±1.1 L/min; P=0.03). Despite higher minute ventilation during hypercapnia in obese subjects, the increase in muscle sympathetic nerve activity was similar in obese and normal-weight subjects. When the inhibitory influence of breathing during hypercapnia was eliminated by apnea, the increase in sympathetic nerve activity in obese subjects (99±16%) was greater than in normal-weight subjects (44±16%; P=0.02). The magnitude of the ventilatory and autonomic responses to hypoxia and the cold pressor test was similar in obese and normal-weight subjects. We conclude that chemoreflex responses to hypercapnia are potentiated in eucapnic obese subjects. In contrast, responses to hypoxia and to the excitatory cold pressor stimulus in obese subjects are similar to those in normal-weight subjects. Thus, obesity is characterized by selective potentiation of central chemoreflex sensitivity. (Hypertension. 1999;33:1153-1158.)

Key Words: hypercapnia ▪ hypoxia ▪ chemoreceptors ▪ sympathetic nervous system ▪ obesity

The chemoreflexes are the dominant control mechanisms regulating ventilatory responses to changes in arterial oxygen and CO₂ content. 1-4 Peripheral chemoreceptors, located in the carotid bodies, respond primarily to hypoxia. 1,2 Central chemoreceptors, located on the ventral surface of the medulla, respond primarily to hypercapnia. 3 Both chemoreceptor mechanisms also exert a powerful influence on neural circulatory control. 5-8 Central and peripheral chemoreflex activation elicit increases in ventilation and sympathetic nerve traffic. 5,9 Increased minute ventilation (Ve) inhibits the sympathetic response to chemoreflex activation. 9,10 Obesity is associated with an increased risk of alveolar hypoventilation and CO₂ retention, 11,12 suggesting that chemoreflex control mechanisms may be disturbed. Surprisingly, the effect of obesity on chemoreflex function has received relatively little attention. Previous studies examining chemoreflex function in obese subjects have examined primarily the ventilatory responses. These studies have reported conflicting results, showing either increased, 13,14 decreased, 15 or normal 16,17 responsiveness to hypoxia in obese subjects. Conflicting results have also been reported in studies examining responses to hypercapnia. Obese subjects have been shown to have either increased 14,17 or decreased 13,15,18 ventilatory responses to hypercapnia. Ventilatory responsiveness to hypercapnia is reduced by weight loss 19,20 and increased by abdominal mass loading, 21 suggesting that obesity might be associated with potentiated central chemoreflex sensitivity. Sympathetic responses to hypoxia or hypercapnia in obese subjects have not been previously studied.

Discrepancies in the results of earlier studies might be explained by a number of factors. First, some of the studies reporting decreased central chemoreflex sensitivity in obesity included hypercapnic subjects with obesity-hypoventilation syndrome. 15,18 Thus, findings of decreased central chemosensitivity in patients with chronically elevated arterial CO₂ levels may represent an adaptation to hypercapnia. Second, chemoreflex sensitivity is significantly influenced by age, 22-24 gender, 14 and hypertension. 6,25 Hence, the absence of control for these variables may be implicated in the lack of consistency in earlier studies. Third, even asymptomatic obese individuals have a high incidence of occult obstructive sleep apnea, 26 which may itself be accompanied by abnormalities in chemoreflex function. 27,28 Thus, undiagnosed sleep apnea in apparently normal obese subjects may obscure any distinctive chemoreflex abnormalities associated with obesity per se.

We tested the hypothesis that chemoreflex function is altered in obesity, independent of such factors as age, gender,
hypertension, and occult sleep apnea. We measured ventilatory, autonomic, and hemodynamic responses to peripheral chemoreceptor activation by hypoxia and to central chemoreceptor activation by hypercapnia in obese subjects, in whom occult sleep apnea was excluded by complete overnight polysomnographic study. These responses were compared with those obtained in normal-weight subjects matched for age and gender. To ensure that any abnormalities in chemoreflex function were specific to the chemoreflexes and did not represent a generalized abnormality in response to excitatory stimuli, we also compared responses to the cold pressor test (CPT), which served as an internal control.29,30

Methods

Subjects
We studied 14 obese subjects (9 men and 5 women; mean age, 40±3 years) and 14 normal-weight subjects matched for gender and age (mean age, 43±2 years). Normal weight was defined as a body mass index (BMI) of ≤24 kg/m² for women and ≤25 kg/m² for men.31 The mean BMI was 35±2 kg/m² for obese subjects and 23±1 kg/m² for normal-weight subjects. None of the subjects was taking any medications or had any chronic disease. Occult obstructive sleep apnea in obese subjects was ruled out by complete overnight polysomnographic study, including electroencephalography, electromyography, electro-oculography, electrocardiography, chest wall movement, nasal and oral air flow, and oxygen saturation. Informed written consent was obtained from all subjects. The study was approved by the institutional Human Subjects Review Committee.

Measurements
Heart rate (HR) was measured continuously by an ECG. Blood pressure was measured each minute by an automatic sphygmomanometer (LifeStat 200, Physio-Control Corp). Oxygen saturation was monitored with a pulse oximeter (Nellcor Inc). End-tidal CO₂ was monitored using a Hewlett-Packard 47210A Capnometer. Vt was determined using a KL Engineering S430 monitor. Subjects breathed through a mouthpiece with a nose clip to ensure exclusive mouth breathing. Sympathetic nerve activity to muscle (MSNA) was recorded continuously by obtaining multunit recordings of postganglionic sympathetic activity to muscle blood vessels, measured from a muscle nerve fascicle in the peroneal nerve posterior to the fibular head as described previously.32

Protocol and Procedures
Subjects were studied in the supine position. The protocol used to determine chemoreflex responses to isocapnic hypoxia and hyperoxic hypercapnia was identical to that used in previous studies.9,10,33 Subjects were exposed to a hypoxic gas mixture to induce peripheral chemoreceptor activation (7% O₂ in N₂ with CO₂ titrated to maintain isocapnia) and to a hypercapnic gas mixture to induce central chemoreflex activation (7% CO₂ and 93% O₂). During hypoxic stimulation of peripheral chemoreceptors, perturbation of central chemoreceptors was minimized by maintenance of isocapnia.10 During hypercapnic stimulation of central chemoreceptors, perturbation of peripheral chemoreceptors was minimized by hyperoxia.9 The sequence of hypoxic and hypercapnic interventions was randomized. At least 15 minutes separated the end of one intervention from the beginning of the next.

Baseline measurements were taken during a 5-minute period of stable ventilation while subjects breathed room air with a mouthpiece. Then, with use of a 3-way valve, subjects were exposed to either hypoxic or hypercapnic stressors for 3 minutes. Average values for the 3-minute period of gas exposure were compared with measurements obtained at baseline. At the end of the hypoxic and hypercapnic exposures, subjects underwent a brief period of voluntary end-expiratory apnea (10 to 15 seconds) to examine the sympathetic responses to chemoreflex activation in the absence of the inhibitory influence of the thoracic afferents. We were not able to obtain stable nerve recordings in 2 subjects (1 obese and 1 normal-weight subject). Consequently, sympathetic responses to hypoxia and hypercapnia were obtained in 13 overweight and 13 normal-weight subjects. Twelve overweight and 13 normal-weight subjects underwent a subsequent CPT. The CPT is a stimulus for ventilation and sympathetic excitation and involves immersing the subject’s hand in ice water for 2 minutes.29,30

Analyses
Sympathetic bursts were identified by careful inspection of the voltage neurogram. The amplitude of each burst was determined, and sympathetic activity was calculated as bursts per minute multiplied by mean burst amplitude and expressed as units per minute. Measurement of nerve activity at baseline before each intervention was expressed as 100%. For the apneas, the first 10 seconds was analyzed, because all subjects were able to maintain apnea for at least 10 seconds at the end of both the hypoxic and hypercapnic exposures. Changes in sympathetic nerve activity were expressed as the percentage of increase from the preceding minute (eg, last minute of hypoxia or hypercapnia).

Changes in integrated MSNA allow evaluation of within-subject changes in sympathetic traffic during the same recording session. Sympathetic activity was also expressed as bursts per minute, which allows comparison of sympathetic discharge between individuals, thus permitting a comparison of MSNA between obese and normal-weight subjects. Demographic data and baseline characteristics were compared using an unpaired t test. Responses to hypoxia, hypercapnia, and the CPT were analyzed by repeated-measures ANOVA with time (baseline versus intervention) as within factor and group (obese versus normal-weight subjects) as between factor. The key variable was the group-by-time interaction. Data are mean±SEM. P<0.05 was considered significant.

Results

Resting Values
Oxygen saturation, blood pressure, HR, and MSNA in overweight subjects were similar to values obtained in normal-weight subjects (Table 1).

Responses to Hypercapnia
The baseline levels and increases of end-tidal CO₂ during hypercapnia were similar in normal-weight and obese subjects (Table 2 and Figure 1). During hypercapnia, HR did not change significantly in either normal-weight or obese subjects (Table 2). Both normal-weight and obese subjects had increases in Vt, blood pressure, and MSNA during hypercapnia. However, the increase in Vt during hypercapnia was significantly greater in obese subjects (Table 2 and Figure 1) (P<0.04).

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Normal-Weight Subjects</th>
<th>Obese Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen saturation, %</td>
<td>98.3±0.3</td>
<td>97.5±0.6</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>113±3</td>
<td>113±3</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>70±3</td>
<td>67±3</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>86±3</td>
<td>83±2</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>60±3</td>
<td>67±3</td>
</tr>
<tr>
<td>MSNA, bursts/min</td>
<td>26±2</td>
<td>23±2</td>
</tr>
</tbody>
</table>

Values are mean±SEM. None of the differences were statistically significant. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; and MAP, mean arterial pressure.

TABLE 1. Baseline Measurements in Normal-Weight and Obese Subjects
Despite higher $\dot{V}E$ values during hypercapnia in obese subjects, the percentage increases in MSNA during hypercapnia were similar in obese and normal-weight subjects (Table 2 and Figure 1). When the inhibitory influence of breathing during hypercapnia was eliminated by apnea, the increase in MSNA in obese subjects was greater than in normal-weight subjects ($P=0.02$).

Responses to Hypoxia
The magnitude of the ventilatory, HR, blood pressure, and MSNA responses to hypoxia was similar in obese and normal-weight subjects (Table 3 and Figure 1). Changes in MSNA in response to apnea during hypoxia were also similar in the 2 groups ($69\pm21\%$ in obese subjects and $83\pm26\%$ in normal-weight subjects).

Effects of CPT
Autonomic, ventilatory, and blood pressure changes during the CPT in obese subjects were not significantly different from those observed in normal-weight subjects (Table 4).

Discussion
The novel findings of this study are, first, that euvapnic obesity is associated with potentiation of the central chemoreflex response to hypercapnia. This is evident in
the increased ventilatory response to hypercapnic breathing. Because the ventilatory response to hypercapnia inhibits the autonomic response, the potentiated sympathetic response becomes evident only during apnea. Second, there is preservation of the normal responses to both peripheral chemoreflex activation and to the CPT. Thus, alteration in chemoreflex function in obese subjects is selective for the central chemoreflex.

Previous studies have reported conflicting results regarding central chemoreflex function in obesity, with some studies reporting decreased, increased normal, or increased ventilatory responses to hypercapnia in obese subjects. Aging is associated with blunting of the ventilatory responses to hypercapnia. In 1 study reporting a decreased hypercapnic ventilatory response in obesity, obese subjects were older than normal-weight subjects. Moreover, most of the obese subjects were women, whereas all the normal-weight control subjects were men. Thus, differences in age and gender distribution between obese and normal-weight subjects may have confounded results of this study.

In the present study, hypercapnic breathing elicited greater ventilatory responses in obese subjects than in normal-weight subjects. Increased ventilation acts as a powerful restraint on the sympathetic response to chemoreflex stimulation. Nevertheless, the increase in sympathetic activity in our obese subjects during hypercapnia was still comparable to that seen in normal-weight subjects despite the higher ventilation. When the inhibitory influence of ventilation was eliminated by apnea, the enhanced sympathetic response to hypercapnia was manifest. Thus, potentiation of the central chemoreflex response in obesity affects both the ventilatory and sympathetic efferent limbs of the reflex. Although increased ventilatory sensitivity might be beneficial in terms of preventing CO2 retention, potentiated sympathetic responsiveness might impose additional circulatory stress.

With respect to peripheral chemoreflex function in obesity, Kunitomo et al and Burki and Baker reported increased ventilatory responses to hypoxia in obese subjects. Interpretation of the former study is difficult, because a large proportion of the obese subjects had sleep-disordered breathing. The latter study did not address the potential influence of sleep apnea. Apparently normal obese subjects have a high prevalence of occult obstructive sleep apnea. Obstructive sleep apnea may itself be accompanied by a selective potentiation of the ventilatory response to hypoxia. Thus, the apparent potentiated peripheral chemoreflex sensitivity in obese subjects may be secondary to obstructive sleep apnea rather than a pathophysiological accompaniment of obesity per se.

Important strengths of this study are, first, that both ventilatory and sympathetic responses to hypercapnia, hypoxia, and the CPT were studied and that ventilatory and sympathetic responses to hypercapnia were increased.

**TABLE 3. Effects of Hypoxia in Normal-Weight and Obese Subjects**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Normal-Weight Subjects</th>
<th>Obese Subjects</th>
<th>Interaction (group x time)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline*</td>
<td>Hypoxia</td>
<td>Baseline*</td>
</tr>
<tr>
<td>Oxygen saturation, %</td>
<td>98.9±0.5</td>
<td>90.0±1.4</td>
<td>98.1±0.4</td>
</tr>
<tr>
<td>End-tidal CO2, mm Hg</td>
<td>37±1</td>
<td>37±1</td>
<td>35±1</td>
</tr>
<tr>
<td>Minute ventilation, L/min</td>
<td>8.0±0.9</td>
<td>11.1±1.3</td>
<td>7.6±0.8</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>60±3</td>
<td>71±3</td>
<td>69±4</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>87±3</td>
<td>90±2</td>
<td>82±3</td>
</tr>
<tr>
<td>MSNA, bursts/min</td>
<td>25±3</td>
<td>27±2</td>
<td>20±2</td>
</tr>
<tr>
<td>Integrated MSNA, %</td>
<td>100</td>
<td>123±7</td>
<td>100</td>
</tr>
</tbody>
</table>

*Values are mean±SEM.
†P values for the interaction term were determined by ANOVA.

**TABLE 4. Effects of Cold Pressor Test (CPT) in Normal-Weight and Obese Subjects**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Normal-Weight Subjects</th>
<th>Obese Subjects</th>
<th>Interaction (group x time)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline*</td>
<td>CPT</td>
<td>Baseline*</td>
</tr>
<tr>
<td>Minute ventilation, L/min</td>
<td>6.8±0.7</td>
<td>8.1±1.0</td>
<td>8.0±0.7</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>57±2</td>
<td>65±3</td>
<td>66±3</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>86±2</td>
<td>99±3</td>
<td>85±3</td>
</tr>
<tr>
<td>Integrated MSNA, %</td>
<td>100</td>
<td>207±26</td>
<td>100</td>
</tr>
</tbody>
</table>

*Values are mean±SEM.
†P values for the interaction term were determined by ANOVA.
autonomic responses to hypercapnia alone were shown to be potentiated in the obese subjects. Thus, our findings suggest a selective chemoreflex abnormality in obesity and do not represent a nonspecific potentiation of responses to stressful stimuli. Second, all subjects were eucapnic and free of any disease, in particular, occult sleep apnea. Third, obese and normal-weight subjects were closely matched for gender, age, and blood pressure. Thus, the potential influence of these confounding variables was eliminated.

Potentiated central chemoreflex drive may serve as a protective mechanism maintaining eucapnia in the presence of an increased respiratory load. This hypothesis is consistent with data from an earlier uncontrolled study by Chapman et al., who reported that the hypercapnic ventilatory response decreased after weight loss in eucapnic obese subjects without sleep-disordered breathing. Eucapnic obese subjects have increased electromyographic responses of the diaphragm to hypercapnia. In contrast, electromyographic responses to hypercapnia in subjects with obesity-hypoventilation syndrome are decreased. The potentiated central chemoreflex drive evident in eucapnic obese subjects may become blunted in subjects who develop alveolar hypoventilation and CO2 retention, perhaps as a result of adaptation of the central chemoreflex to chronic hypercapnia. Alternatively, absence of potentiation of central chemoreflex in obesity may result in consequent progression to alveolar hypoventilation and CO2 retention.

Although the mechanism underlying the selective potentiation of the responses to hypercapnia is unknown, a recent study by Tankersley et al. provides a rationale for hypothesizing that modulation of the central chemoreflex by leptin may be implicated. In studies in ob/ob mice, these investigators reported a marked impairment in ventilatory responses to hypercapnia. ob/ob mice are leptin deficient. In contrast, obese humans have markedly increased levels of leptin. We speculate that leptin may be important in modulation of the central chemoreflex so that, first, an absolute deficiency of leptin (in ob/ob mice) is accompanied by a blunted chemoreflex response to hypercapnia and, second, the increased leptin in obese humans is linked to a potentiated chemoreflex response to hypercapnia. We further speculate that the increased leptin in obese humans confers protection from obesity-related hypoventilation and hypercapnia and hence a possible survival advantage.

In conclusion, these data demonstrate a potentiation of ventilatory and sympathetic responses to hypercapnia in eucapnic obese subjects. In contrast, responses to hypoxia and responses to the excitatory cold pressor stimulus in obese subjects are similar to those in normal-weight subjects. Thus, obesity is characterized by selective potentiation of central chemoreflex sensitivity.

Acknowledgments

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References

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