Ventilatory responses to hypercapnia and hypoxia in relatives of patients with the obesity hypoventilation syndrome

R Jokic, T Zintel, G Sridhar, C G Gallagher, M F Fitzpatrick

Abstract

Background—It is unclear why some morbidly obese individuals have waking alveolar hypoventilation while others with similar obesity do not. Some evidence suggests that patients with the obesity hypoventilation syndrome (OHS) may have a measurable premorbid impairment of ventilatory chemoresponsiveness. Such an impairment of ventilatory chemoresponsiveness in OHS, however, may be an acquired and reversible consequence of severe obstructive sleep apnoea (OSA). We hypothesised that, in patients with OHS who do not have coincident severe OSA, there may be a familial impairment in ventilatory responses to hypoxia and hypercapnia.

Methods—Sixteen first degree relatives of seven patients with OHS without severe OSA (mean (SD) age 40 (16) years, body mass index (BMI) 30 (6) kg/m²) and 16 subjects matched for age and BMI without OHS or OSA were studied. Selection criteria included normal arterial blood gas tensions and lung function tests and absence of sleep apnoea on overnight polysomnography. Ventilatory responses to isocapnic hypoxia and to hypercapnia were compared between the two groups.

Results—The slope of the ventilatory response to hypercapnia was similar in the relatives (mean 2.33 l/min/mm Hg) and in the control subjects (2.12 l/min/mm Hg), mean difference 0.2 l/min/mm Hg, 95% confidence interval (CI) for the difference –0.5 to 0.9 l/min/mm Hg, p=0.5. The hypoxic ventilatory response was also similar between the two groups (slope factor A: 379.1 l/min · mm Hg for relatives and 373.4 l/min · mm Hg for controls; mean difference 5.7 l/min · mm Hg; 95% CI –282 to 293 l/min · mm Hg, p=0.7; slope of the linear regression line of the fall in oxygen saturation and increase in minute ventilation: 2.01 l/min/% desaturation in relatives, 1.15 l/min/% desaturation in controls; mean difference 0.5 l/min/% desaturation; 95% CI –1.7 to 0.7 l/min/% desaturation, p=0.8).

Conclusion—There is no evidence of impaired ventilatory chemoresponsiveness in first degree relatives of patients with OHS compared with age and BMI matched control subjects.

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Keywords: obesity hypoventilation syndrome; ventilatory response; hypoxia; hypercapnia

Remarkably few studies have addressed the question of why alveolar hypoventilation develops in some obese individuals but not in others. Two major theories have been advanced since Burwell and colleagues originally described a case.1 The first theory is that the excessive mechanical load caused by obesity places an overwhelming burden on the inspiratory muscles, leading to hypoventilation. 2 This theory is supported by the fact that substantial weight loss in these patients is often attended by a marked improvement in their clinical state and in their arterial blood gas tensions.1 3 4 Although attractive, this hypothesis has some important contradictions. There is a very poor correlation between the degree of obesity and the extent of hypoventilation5 3 and most very obese individuals do not develop alveolar hypoventilation.5 6 In addition, although obesity is associated with an increased elastic load to the respiratory system,7 8 9 no correlation exists between the degree of obesity (body mass index) and the compliance of the chest wall.10 11 Indeed, most patients with obesity hypoventilation syndrome (OHS) can hyper-ventilate when requested and normalise their arterial carbon dioxide tension (PaCO₂).12 Thus, the mechanical disadvantage of obesity alone does not provide an adequate explanation for hypoventilation in these patients.

The second theory proposes that alveolar hypoventilation is a consequence of blunted ventilatory drive.13 Indeed, several studies have shown that patients with OHS have significantly reduced hypoxic and hypercapnic ventilatory drives compared with normal subjects.14 16 However, it is impossible to discern from these studies whether the loss of ventilatory chemoresponsiveness was a primary phenomenon or secondary to chronic hypoxia and hypercapnia.6 Sampson and Grassino17 demonstrated impairment of hypercapnic ventilatory responses in eucapnic massively obese subjects who had previously suffered transient hypercapnia at the time of a respiratory insult compared with carefully matched controls who had never been hypercapnic. This finding suggested that a measurable premorbid impairment in ventilatory chemoresponsiveness may exist in patients with OHS, such that they fail to compensate appropriately for the mechanical disadvantage imposed on the respiratory system by massive weight gain.17 18
If such a premorbid impairment in ventilatory chemoresponsiveness among patients with OHS exists, as suggested by the work of Sampson and Grassino, it could have a genetic or familial basis. Indeed, similar familial impairments in chemoresponsiveness have been reported in patients with chronic obstructive pulmonary disease (COPD) and asthma. We therefore decided to compare the hypercapnic and hypoxic ventilatory drives of healthy first degree relatives of patients with OHS and matched normal subjects. To avoid the confounding effect of an acquired impairment in ventilatory chemoresponsiveness as a consequence of severe obstructive sleep apnoea (OSA), we chose to exclude from the study probands with severe OSA.

**Methods**

**SUBJECTS**

Group 1 consisted of 16 healthy adult first degree relatives (10 siblings, six offspring) of seven patients with OHS. First degree relatives were recruited by canvassing index patients. Group 2 comprised 16 healthy subjects of similar age and BMI to those in group 1 who had no family history of OHS. This control group was recruited by newspaper advertisement and screened by interview.

The demographic characteristics of all subjects are shown in table 1. Each subject underwent a history and physical examination. The smoking history, alcohol and caffeine consumption, and any medication intake, in particular, were documented. All subjects were healthy at the time of the study and no subject was taking medication (stimulant, sedative, bronchodilator, or steroid) which might influence ventilatory chemoresponsiveness. There were seven current smokers in group 1 and two in group 2.

The index cases consisted of seven patients with OHS of mean age 51 years (range 32–70) who presented to the respiratory clinic at Royal University Hospital, Saskatoon (mean (SD) BMI 44.6 (9.4) kg/m²), arterial blood gas tension on room air (Pao), 8.9 (1.5) kPa, PaCO₂, 6.9 (1.2) kPa, oxygen saturation 93 (2)%, pH 7.4 (0.05). All patients underwent diagnostic overnight polysomnography at the Sleep Disorders Centre, Royal University Hospital, Saskatoon (mean (SD) apnoea-hypopnoea index (AHI) 14 (11), range 4–35) and lung function tests (forced vital capacity (FVC) 66 (15)% predicted, forced expiratory volume in one second (FEV₁) 70 (16)% predicted, total lung capacity (TLC) 74 (13)% predicted, functional residual capacity (FRC) 71 (2)% predicted).

**STUDY DESIGN**

Subjects were asked to refrain from caffeine and tobacco consumption on the day of the study until after completion of lung function tests, ventilatory response measurements, and arterial blood gas sampling.

Pulmonary function tests were performed in order to exclude mechanical limitation of the respiratory system. Static lung volumes, airway resistance, dynamic lung volumes, and transfer factor were measured on each subject during a single sitting after a period of 30 minutes rest (6200 automated body plethysmograph, Sensormedics, CA, USA). Respiratory muscle strength was assessed by measuring maximal inspiratory and expiratory pressures (Instrumentation Industries, PA, USA) and an arterial blood sample was obtained for blood gas analysis.

**Ventilatory response measurements**

The resting breathing parameters were determined after 10 minutes of quiet breathing through a mouthpiece. Flow was measured using a heated pneumotachograph (Fleisch #3). Heart rate and oxygen saturation were continuously monitored (ear pulse oximeter and ECG monitor; Nellcor, CA, USA). End tidal oxygen and carbon dioxide were continuously sampled at the mouth and analysed using a mass spectrometer with a five channel strip chart recorder (MGA 2000; Airspec, Kent, UK).

Ventilatory responses were measured using rebreathing techniques. The ventilatory response to hypercapnia was determined using the hyperoxic hypercapnic rebreathing technique of Read. A seven litre bag was filled with a gas mixture (initial composition 93% oxygen and 7% carbon dioxide). The volume of the gas mixture was set to one litre above the subjects’ vital capacity. The subjects were asked to breathe quietly through the mouthpiece for two minutes and then were switched onto the bag at the end of normal expiration. The test was continued for five minutes or until either the subject stopped voluntarily because of discomfort or the end tidal carbon dioxide pressure (PETCO₂) reached 70 mm Hg.

The slope (S), correlation coefficient (R), and intercept (B) of the line relating minute ventilation to PETCO₂, were used to characterise a particular subject’s response according to the equation

\[ \text{VE} = S \left( \text{PETCO}_2 - B \right) \]

where \( \text{VE} \) is the minute ventilation, \( S \) is the slope of the \( \text{VE} - \text{PETCO}_2 \) regression line in l/min/mm Hg, and \( B \) is the extrapolated intercept on the abscissa in mm Hg.

The ventilatory response to hypoxia was determined by the isocapnic hypoxic rebreathing technique of Rebuck and Campbell. The subjects were asked to rebreathe a gas mixture...
The oxygen saturation fell below 75\%, end tidal oxygen pressure (PET\(_{O_2}\)) decreased to 50 mm Hg, or when the subject voluntarily stopped the test.

The relationship between \(V_\text{E}\) and alveolar PO\(_2\) was assumed to be hyperbolic and the ventilatory response to hypoxia was calculated from the formula:

\[
V_\text{E} = V_0 + A/(\text{PETO}_2 - 32)
\]

where \(V_0\) is the minute ventilation when PET\(_{O_2}\) is infinite, factor A is the slope factor characteristic to the shape of the hyperbola in l/min • mm Hg, and 32 is the asymptote for PET\(_{O_2}\) in mm Hg when minute ventilation is infinite. Parameter A was also calculated as the slope between the change in minute ventilation and change in oxygen saturation in l/min/1% desaturation:

\[
A = ΔV_\text{E}/ΔSat\_O_2
\]

The ventilatory responses were standardised for body surface area (BSA) and FVC.

### Results

Pulmonary function, arterial blood gas data, and breathing parameters at rest are presented in tables 2 and 3, respectively, and data from the overnight polysomnography study are presented in table 4. There were no significant differences in any of the variables listed between the relatives of patients with OHS and the control subjects.

Figures 1 and 2 present the group mean data for hypercapnic and hypoxic ventilatory responses for the relatives and control subjects. There were no statistically significant differences in the ventilatory responses to hypercapnia between the two groups as measured by slope factor S (mean 2.33 l/min/mm Hg in relatives, 2.12 l/min/mm Hg in controls; mean difference 0.2 l/min/mm Hg, p=0.5; fig 2). The values of the intercept (B) of the ventilatory response line were also similar between the two groups (relatives 41.9 mm Hg, controls 42.6 mm Hg; mean difference 0.72 mm Hg, 95% CI –3.1 to 4.5, p=0.7).

Similarly, there were no significant differences between groups in the ventilatory responses to hypoxia as measured by slope factor A (mean 379.1 l/min/mm Hg in relatives, 373.4 l/min/mm Hg in controls; mean difference 5.7 l/min/mm Hg, 95% CI –6 to –0.5, p=0.07; fig 3). The range of hypercapnic and hypoxic ventilatory responses observed in the two groups is shown in fig 3.
Table 5  Mean (SE) ventilatory responses to hypercapnia and hypoxia after standardising for body surface area and forced vital capacity

<table>
<thead>
<tr>
<th></th>
<th>Relatives</th>
<th>Controls</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>S/BSA (l/min/mmHg/m²)</td>
<td>0.84 (0.08)</td>
<td>0.77 (0.08)</td>
<td>0.6</td>
</tr>
<tr>
<td>A/BSA (l/min • mmHg/m²)</td>
<td>134 (28.8)</td>
<td>133.4 (23.9)</td>
<td>1.0</td>
</tr>
<tr>
<td>Vs/Sao₂/BSA (l/min/%)</td>
<td>0.70 (0.14)</td>
<td>0.54 (0.08)</td>
<td>0.4</td>
</tr>
<tr>
<td>S/FVC (l/min/mmHg/l)</td>
<td>0.57 (0.05)</td>
<td>0.55 (0.05)</td>
<td>0.8</td>
</tr>
<tr>
<td>A/FVC (l/min • mmHg/l)</td>
<td>89.0 (15.8)</td>
<td>87.8 (13.4)</td>
<td>0.9</td>
</tr>
<tr>
<td>Vs/Sao₂/FVC (l/min/%)</td>
<td>0.46 (0.08)</td>
<td>0.38 (0.08)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

S = slope factor for the ventilatory response to hypercapnia; BSA = body surface area; A = hypoxic ventilatory response; Vs = minute ventilation; Sao₂ = oxygen saturation; FVC = forced vital capacity.

There were no differences in acid-base chemosensitivity for body surface area and forced vital capacity.
try between the two groups and none of the subjects had a history of endurance athletics or residence at high altitudes. We attempted to control for other factors that might influence the hypoxic and hypercapnic ventilatory responses by comparing two groups of subjects with similar anthropometric characteristics, and by standardising the ventilatory responses for body surface area and lung volume.

Twin studies have suggested that the wide variability in respiratory chemosensitivity can be explained, at least partly, by genetic factors, although there is still some controversy concerning the role of genetic factors in the hypercapnic ventilatory response.34–37 In recent years major advances have been made in identifying the components of the homeostatic system that regulate body weight, including several of the genes responsible for animal and human obesity. The key element of this physiological system is the hormone leptin which acts on nerve cells in the hypothalamus to suppress appetite. Human obesity, similar to obesity in wild type mice, causes a variable increase in circulating leptin.43 Studies in genetically obese mice (ob/ob) have shown that genetic determinants related to the ob locus influence hypercapnic ventilation before the emergence of pronounced obesity.35 Moreover, in the genetic mouse model of obesity prolonged treatment with leptin attenuated the respiratory complications associated with the obese phenotype, including rapid breathing pattern at baseline, diminished lung compliance, and abnormal respiratory muscle adaptations.44 A recent study from the same group of authors has shown that the obese mouse which lacks circulating leptin also exhibits respiratory depression and increased PaCO₂.45 However, a three day infusion of leptin significantly increased minute ventilation during both sleep and wakefulness, independently of food intake, weight, and CO₂ production, indicating stimulation of central respiratory control centres. The authors postulated that a relative deficiency in leptin, or resistance to leptin, may play an important part in conditions with disordered control of breathing such as OHS.46 47

There is considerable evidence to suggest that the hypercapnic ventilatory response is, at least in part, behaviourally modulated in conscious humans.44–46 A longitudinal analysis in a normal population showed that the individual values of the hypoxic response measured after an interval of 8–10 years were significantly correlated but that this was not so for the hypercapnic response, also suggesting that, in the long term, the latter is more subject to influence from extrinsic factors than the former.48 Thus, it is possible that the influence of genetic factors subsides in adults, especially the influence on the hypercapnic response, and that environmental factors predominate. This is one possible explanation for the negative findings in the current adult study.

Kawakami et al49 reported that the ventilatory responses to hypoxia are significantly higher in monogynotic twin smokers than in non-smoking pairs. All smokers in the current study (seven relatives, two controls) refrained from smoking on the day of the study in order to minimise this potential confounding effect.

As in several earlier studies, this study has failed to elucidate a disproportionate familial effect in the aetiology of OHS, a finding which supports the concept of a multifactorial aetiology for this disorder.40 Ventilatory muscle dysfunction, abnormal load responsiveness, impaired central respiratory drive, and repeated airway occlusion during sleep (if there is coexisting OSA) are all possible pathophysiological elements in OHS, but the precise contribution of each still remains to be elucidated. Furthermore, patients with OHS may have additional problems such as airway limitation due to smoking or asthma and ventilation/perfusion mismatch due to the restrictive effect of obesity which may contribute to alveolar hypoventilation. Mechanical factors (ventilatory muscle dysfunction, susceptibility to muscle fatigue, decreased ventilatory efficiency caused by changes in thoracic mechanics) have been suggested to play a significant part in alveolar hypoventilation in OHS.49 A significant improvement in the hypercapnic drive occurring within 24 hours of initiating CPAP treatment in some patients may be consequent belief of ventilatory muscle fatigue.50 Following treatment (CPAP or tracheotomy) many patients with OHS return to eucapnia without a change in the hypercapnic ventilatory response, further suggesting that some abnormality rather than, or in addition to, altered ventilatory drive must be present.51 However, these mechanical derangements alone are not enough to account for the disorder. Lyons and Huang52 made the important observation that administration of the respiratory stimulant progesterone could normalise the PaCO₂ in patients with OHS by improving respiratory drive without altering respiratory mechanics. Furthermore, when asked, most patients with OHS can voluntarily hyperventilate to eucapnia.53

A criticism of the current study is that four pairs of subjects were not matched by sex. Although women tend to have lower ventilatory responses than men, these differences are usually attributed to the body size54 and seem to decline with advancing age.55

The sample size for this study was based on data from Mountain and colleagues56 who found significant differences in the ventilatory response to hypercapnia between offspring of eucapnic patients with COPD (2.1 (0.37) l/min/mm Hg) and those of hypercapnic patients with COPD (1.3 (0.14) l/min/mm Hg). Our study was powered to detect a true difference in ventilatory chemosensitivity between relatives and controls no larger than half of that previously reported,15 and had a statistical power of 90% to detect a significant difference in ventilatory responses between the relatives and the control group (α=0.05).

We conclude that there is no evidence of impaired ventilatory chemosensitivity in relatives of patients with OHS compared with age and BMI matched control subjects. This finding does not support the hypothesis that a
genetic impairment in ventilatory chemosensitivity underlies the development of OHS.

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