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 hypercapnic 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
If such a premorbid impairment in ventilatory chemoresponsiveness among patients with OHS exists, as suggested by the work of Sampson and Grassino,\(^{12}\) 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)\(^{19–21}\) and asthma.\(^{22}\) 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) 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 (FEV\(_1\)) 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; Nelcor, 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.\(^{21}\) 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 test was continued for five minutes or until either the subject stopped voluntarily because of discomfort or the end tidal carbon dioxide pressure (PETCO\(_2\)) reached 70 mm Hg.

The slope (S), correlation coefficient (R), and intercept (B) of the line relating minute ventilation to PETCO\(_2\) were used to characterise a particular subject’s response according to the equation

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

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 Reubuck and Campbell.\(^{24}\) The subjects were asked to rebreathe a gas mixture...
containing 7% carbon dioxide, 23% oxygen, and balance nitrogen. The partial pressure of carbon dioxide was held constant throughout the study using a carbon dioxide absorber (a portion of the gas in the rebreathing bag was drawn through the absorber and returned to the bag, fig 1). The test was discontinued when the oxygen saturation fell below 75%, end tidal oxygen pressure (PETO₂) decreased to 50 mm Hg, or when the subject voluntarily stopped the test.

The relationship between VE and alveolar PO₂ was assumed to be hyperbolic and the ventilatory response to hypoxia was calculated from the formula:

$$V_E = V_0 + A/(PETO_2 - 32)$$

where V₀ is the minute ventilation when PETO₂ 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 PETO₂ 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:

$$A = \Delta V_E/\Delta S_{AR}$$

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

**DATA ANALYSIS**

The differences between the groups (relatives versus controls) were analysed using the Wilcoxon rank test for data not normally distributed or the paired t test for normally distributed data.

**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, 95% confidence interval (CI) for the difference -0.5 to 0.9 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 -282 to 293 l/min • mm Hg, p=0.7) or the slope of the linear regression line that describes the relationship between the fall in oxygen saturation and the increase in minute ventilation (relatives 2.01 l/min/% desaturation, controls 1.15 l/min/% desaturation; mean difference 0.86 l/min/% desaturation; 95% CI -0.7 to 0.7 l/min/% desaturation, p=0.8; fig 3). The range of hypercapnic and hypoxic ventilatory responses observed in the two groups is shown in fig 3.
ventilatory response; $V_S =$ slope factor for the ventilatory response to hypercapnia; $BSA =$ body surface area; $A =$ hypoxic ventilatory responses to hypercapnia and hypoxia.

Figure 2 Hypoxic ventilatory responses in the relatives of patients with obesity hypoventilation syndrome (OHS) and the control subjects.

Figure 3 Individual values of the hypercapnic and hypoxic ventilatory responses.

Standardising the ventilatory responses for $BSA$ and $FVC$, known determinants of ventilatory responses, did not influence the statistical significance for the differences in the chemosensitivity between the two study groups, as shown in table 5.

**Discussion**

The results of this study show no significant differences in ventilatory responses to hypercapnia or hypoxia between the first degree relatives of patients with OHS and a control group of healthy adult subjects. Contrary to our hypothesis, this finding provides no support for the concept that a familial impairment in ventilatory chemosensitivity underlies the development of OHS.

OHS is characterised by obesity and awake hyperventilation in the absence of an alternative neuromuscular, mechanical, or metabolic explanation for hypoventilation. The relationship between obesity, depressed central respiratory drive, and OSA is complex. Obesity, excessive daytime somnolence, and loud snoring commonly occur in patients with both OHS and OSA, and the clinical descriptions of these two disorders often overlap.26 Daytime alveolar hypoventilation has been clearly described in patients with obesity and severe OSA and, in the majority of such patients, is reversible with treatment of OSA.27 28 The ventilatory response to hypercapnia has been reported to be reduced in obese patients with OSA compared with obese patients without OSA.29 However, in a significant proportion of patients with OHS alveolar hypoventilation during wakefulness persists despite adequate treatment of OSA.30 Such patients require augmentation of ventilation during sleep, rather than simply relief of upper airway obstruction, to reverse daytime hypoventilation.31 Thus, patients with OHS can be divided into two subsets—those with co-existing severe OSA and those without severe OSA. OHS in the presence of severe OSA may have a different aetiology from OHS in the absence of severe OSA because the former patients may revert to eucapnia with treatment of the OSA alone.27 28 Hence, OHS in the presence of severe OSA may be an acquired and reversible phenomenon resulting from upper airway obstruction at night rather than the result of a specific familial/genetic predisposition to hypoventilation. We reasoned that the other subset of OHS patients—obese patients with OHS that could not be explained on the basis of severe OSA—would be the group most likely to have a familial or genetic predisposition to OHS. This study therefore determined whether a familial defect in the ventilatory response to hypoxia or hypercapnia exists in this latter subset of patients.

Several important points must be taken into consideration when interpreting the results of this study. Individual respiratory chemosensitivity has a broad distribution among normal subjects.31 32 This wide intersubject variability, which was also apparent in the current study of 32 healthy adult subjects, has been attributed to marked differences in physical characteristics and lung mechanics. Some of the subjects in both groups showed very low ventilatory responses, similar to those previously reported in normal subjects.25 32 We observed no familial clustering among subjects with low ventilatory responses in the current study, and no tendency towards low respiratory chemosensitivity in the relatives. Factors which influence the respiratory chemosensitivity include age, sex, body size, changes in physical characteristics, metabolic rate, acid-base status, high altitude residence, and smoking habits.25 31 33 There were no differences in acid-base chemis-

![Image](image_url)
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 re-
bsponses 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 con-
cerning the role of genetic factors in the hyper-
capnic ventilatory response.44–47

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.44 Studies in 
genetically obese mice (ob/ob) have shown that 
leptin, and the presence of the hormone 
leptin, may play an important part in condi-
tions with disordered control of breathing such 
as OHS.40 A significant improvement in the 
hypercapnic drive occurring within 24 hours of 
initiating CPAP treatment in some patients 
may be caused by normalization of ventilatory 
muscle fatigue.45 Following treatment (CPAP 
or tracheotomy) many patients with OHS 
return to eucapnia without a change in the 
hypercapnic ventilatory response, further sug-
gesting that some abnormality rather than, or 
in addition to, altered ventilatory drive must be 
present.45 However, these mechanical derange-
ments alone are not enough to account for the 
disorder. Lyons and Huang46 made the impor-
tant observation that administration of the 
respiratory stimulant progesterone could normal-
ise the PaCO2 in patients with OHS by 
improving respiratory drive without changing 
respiratory mechanics. Furthermore, when 
asked, most patients with OHS can voluntarily 
hyerventilate to eucapnia.12

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 usu-
ally attributed to the body size77 and seem to 
decline with advancing age.12

The sample size for this study was based on 
data from Mountain and colleagues9 who found 
significant differences in the ventilatory 
response to hypercapnia between offspring of 
eucapnia patients with COPD (2.1 (0.37) l/
min/mm Hg) and those of hypercapnic pa-
tients with COPD (1.3 (0.14) l/min/mm Hg). 
Our study was powered to detect a true differ-
ce in ventilatory chemosensitivity between 
relatives and controls no larger than half of that 
previously reported,19 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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