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/m^2) 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 hyperoxic 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.**

(*Thorax* 2000;**55**:940–945)

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 hypoventilation[2 5] 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,[6–9] 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 hyperventilate when requested and normalise their arterial carbon dioxide tension ($Paco_2$).[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 Grassino[17] 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]

Division of Respiratory Medicine, Royal University Hospital, Saskatoon, Saskatchewan, Canada S7N 0W8
R Jokic
T Zintel
C G Gallagher
M F Fitzpatrick

Regina Health District, Regina, Saskatchewan, Canada
G Sridhar

Correspondence to:
Dr R Jokic, Department of Psychiatry, Royal University Hospital, Saskatoon, Saskatchewan, Canada, S7N 0W8
rjokic@sk.sympatico.ca

Received 5 November 1999
Returned to authors 13 March 2000
Revised version received 5 June 2000
Accepted for publication 8 August 2000

If such a premorbid impairment in ventilatory chemoresponsiveness among patients with OHS exists, as suggested by the work of Sampson and Grassino,[17] 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) BMI 44.6 (9.4) kg/m^2), arterial blood gas tensions on room air (Pa_{O_2} 8.9 (1.5) kPa, Pa_{CO_2} 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 (FEV_1) 70 (16)% predicted, total lung capacity (TLC) 74 (13)% predicted, functional residual capacity (FRC) 71 (2)% predicted).

Table 1 Individual anthropometric data

	Relatives			*Controls*		
Subject	*Sex*	*Age (years)*	*BMI (kg/m^2)*	*Sex*	*Age (years)*	*BMI (kg/m^2)*
1	M	20	31.0	M	23	31.4
2	M	23	22.8	M	21	23.8
3	M	25	25.2	M	28	28.7
4	F	29	28.7	F	25	21.7
5	F	30	29.3	F	31	25.1
6	F	29	32.0	M	35	34.0
7	M	32	45.4	F	35	45.9
8	F	33	30.8	M	35	30.0
9	F	36	24.5	F	37	25.3
10	M	40	24.2	M	42	23.0
11	F	44	24.2	F	48	26.4
12	F	45	35.4	F	50	36.9
13	F	48	31.2	F	49	33.5
14	F	63	27.5	F	63	28.6
15	M	68	30.1	F	65	27.5
16	F	69	37.7	F	71	34.5

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.[23] 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 (P_{ETCO_2}) reached 70 mm Hg.

The slope (S), correlation coefficient (R), and intercept (B) of the line relating minute ventilation to P_{ETCO_2} were used to characterise a particular subject's response according to the equation

$$\dot{V}_E = S\ (P_{ETCO_2} - B)$$

where $\dot{V}_E$ is the minute ventilation, S is the slope of the $\dot{V}_E - P_{ETCO_2}$ 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.[24] The subjects were asked to rebreathe a gas mixture

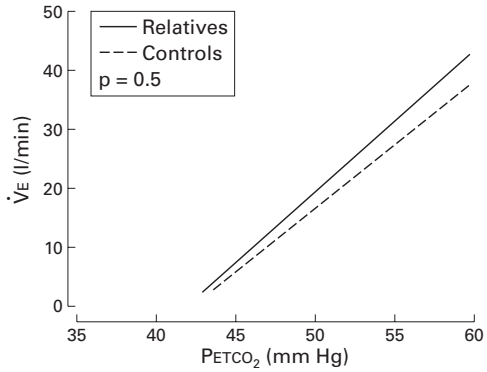

Figure 1 Hypercapnic ventilatory responses in the relatives of patients with obesity hypoventilation syndrome (OHS) and the control subjects.

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 (P_{ETO_2}) decreased to 50 mm Hg, or when the subject voluntarily stopped the test.

The relationship between $\dot{V}_E$ and alveolar P_{O_2} was assumed to be hyperbolic and the ventilatory response to hypoxia was calculated from the formula:

$$\dot{V}_E = \dot{V}_O + A/(P_{ETO_2} - 32)$$

where $\dot{V}_O$ is the minute ventilation when P_{ETO_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 P_{ETO_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:

$$A = \Delta\dot{V}_E/\Delta Sat\ O_2$$

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

Table 2 Mean (SD) arterial blood gas tensions and lung function tests

	Relatives	*Controls*
Pa_{O_2} (kPa)	11.9 (1.2)	11.6 (0.9)
Pa_{CO_2} (kPa)	5.1 (0.5)	5.3 (0.4)
O_2 saturation (%)	97 (1)	96 (1)
pH	7.39 (0.02)	7.40 (0.02)
FVC (% pred)	99 (11)	100 (16)
FEV_1 (% pred)	104 (10)	102 (20)
FEV_1/FVC (% pred)	82 (7)	78 (8)
TLC (% pred)	100 (15)	105 (13)
RV (% pred)	93 (32)	110 (42)
FRC (% pred)	89 (17)	104 (32)
T_{LCO} (%pred)	78 (15)	86 (12)
T_{LCO}/V_T (% pred)	91 (19)	94 (15)
MIP (% pred)	99 (32)	105 (19)
MEP (% pred)	59 (15)	64 (15)

Pa_{O_2}, Pa_{CO_2} = arterial oxygen and carbon dioxide tensions; FVC = forced vital capacity; FEV_1 = forced expiratory volume in one second; TLC = total lung capacity; RV = residual volume; FRC = functional residual capacity; T_{LCO} = carbon monoxide transfer factor; V_T = tidal volume; MIP = maximum inspiratory pressure; MEP = maximum expiratory pressure.

Table 3 Mean (SD) breathing parameters at rest

	Relatives	*Controls*
T_I (min)	1.73 (0.38)	1.69 (0.48)
T_E (min)	2.76 (0.62)	2.39 (0.83)
T_I/T_{TOT}	0.39 (0.42)	0.44 (0.30)
f	13.72 (3.00)	15.93 (4.66)
$\dot{V}_E$ (l/min)	10.27 (2.14)	11.90 (2.35)
P_{ETCO_2} (mmHg)	35.16 (4.39)	37.03 (4.10)

T_I = inspiratory time; f = breathing frequency; T_E = expiratory time; $\dot{V}_E$ = minute ventilation; P_{ETCO_2} = end tidal CO_2 pressure.

Table 4 Mean (SD) sleep architecture and respiratory variables at overnight polysomnography in the relatives and control subjects

	Relatives	*Controls*	*p value*
Stage 1 (% TST)	10.7 (7.2)	6.4 (4.1)	0.01
Stage 2 (% TST)	47.6 (11.1)	48.6 (7.9)	0.8
Slow wave sleep (% TST)	21.5 (9.6)	21.6 (7.3)	1.0
REM (% TST)	20.3 (7.0)	23.4 (6.9)	0.2
Sleep efficiency (TST/TRT)	79.3 (18.9)	86.1 (7.5)	0.2
Apnoea/hypopnoea index (AHI)	3.8 (5.1)	2.9 (1.9)	0.5
Mean oxygen saturation non-REM sleep (%)	95 (1)	95 (1)	0.1
Minimum oxygen saturation non-REM sleep (%)	90 (3)	90 (3)	0.9
Mean oxygen saturation REM sleep (%)	95 (2)	96 (2)	0.8
Minimum oxygen saturation REM sleep (%)	88 (4)	89 (2)	0.1

TRT = total recorded time; TST = total sleep time.

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 0.5 l/min/% desaturation; 95% CI –1.7 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.

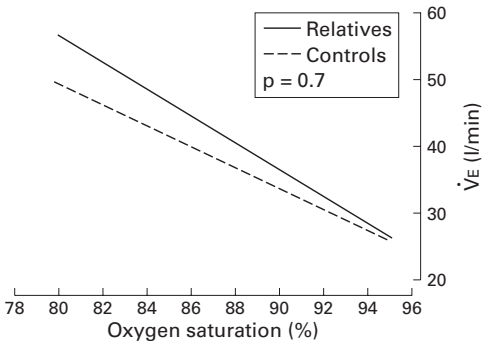

Figure 2 Hypoxic ventilatory responses in the relatives of patients with obesity hypoventilation syndrome (OHS) and the control subjects.

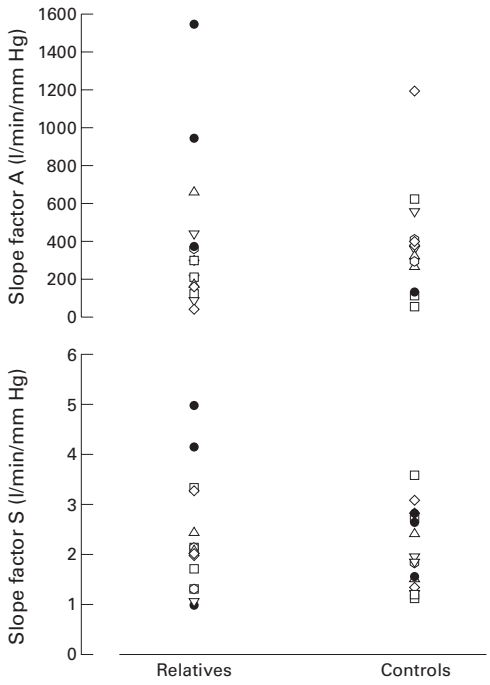

Figure 3 Individual values of the hypercapnic and hypoxic ventilatory responses.

Standardising the ventilatory responses for BSA and FVC, known determinants of ventilatory responses,[25] did not influence the statistical significance for the differences in the chemoresponsiveness 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 chemoresponsiveness underlies the development of OHS.

OHS is characterised by obesity and awake hypercapnia 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.[30] 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-

Table 5 Mean (SE) ventilatory responses to hypercapnia and hypoxia after standardising for body surface area and forced vital capacity

	Relatives	*Controls*	*p value*
S/BSA (l/min/mmHg/m^2)	0.84 (0.08)	0.77 (0.08)	0.6
A/BSA (l/min • mmHg/m^2)	134 (28.8)	133.4 (23.9)	1.0
$\dot{V}_E/Sa_{O_2}$/BSA (l/min/%/m^2)	0.70 (0.14)	0.54 (0.08)	0.4
S/FVC (l/min/mmHg/l)	0.57 (0.05)	0.55 (0.05)	0.8
A/FVC (l/min • mmHg/l)	89.0 (15.8)	87.8 (13.4)	0.9
$\dot{V}_E/Sa_{O_2}$/FVC (l/min/%/l)	0.46 (0.08)	0.38 (0.08)	0.5

S = slope factor for the ventilatory response to hypercapnia; BSA = body surface area; A = hypoxic ventilatory response; $\dot{V}_E$ = minute ventilation; Sa_{O_2} = oxygen saturation; FVC = 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.[38] 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.[39] Furthermore, 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.[40] 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 $Paco_2$.[41] However, a three day infusion of leptin significantly increased minute ventilation during both sleep and wakefulness, independently of food intake, weight, and CO_2 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.[41 42]

There is considerable evidence to suggest that the hypercapnic ventilatory response is, at least in part, behaviourally modulated in conscious humans.[43–45] 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.[46] 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 al*[47] reported that the ventilatory responses to hypoxia are significantly higher in monozygotic 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.[48] 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 consistent with the relief of ventilatory muscle fatigue.[28] 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.[50] However, these mechanical derangements alone are not enough to account for the disorder. Lyons and Huang[51] made the important observation that administration of the respiratory stimulant progesterone could normalise the $Paco_2$ in patients with OHS by improving respiratory drive without altering respiratory mechanics. Furthermore, when asked, most patients with OHS can voluntarily hyperventilate 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 usually attributed to the body size[47] and seem to decline with advancing age.[52]

The sample size for this study was based on data from Mountain and colleagues[19] 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,[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 chemoresponsiveness 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 chemoresponsiveness underlies the development of OHS.

This work was supported by a grant from the Saskatchewan Lung Association. The Saskatchewan Lung Association provided salary support to Drs Jokic and Sridhar in the form of a Fellowship and Professorship, respectively.

1 Burwell CS, Robin ED, Whaley RF, *et al*. Extreme obesity associated with alveolar hypoventilation: a pickwickian syndrome. *Am J Med* 1956;**21**:811–8.
2 Sharp JT, Henry JP, Sweant SK, *et al*. Effects of mass loading the respiratory system in man. *J Appl Physiol* 1964;**19**:959–66.
3 Sugerman HJ, Fairman RP, Sood RK, *et al*. Long-term effects of gastric surgery for treating respiratory insufficiency of obesity. *Am J Clin Nutr* 1992;**55**:597–601S.
4 Thomas PS, Cowen ERT, Hulands G, *et al*. Respiratory function in the morbidly obese before and after weight loss. *Thorax* 1989;**44**:382–6.
5 Bedell GN, Wilson WR, Seebohm PM. Pulmonary function in obese persons. *J Clin Invest* 1958;**37**:1049–61.
6 Rochester DF, Enson Y. Current concepts in the pathogenesis of the obesity-hypoventilation syndrome. Mechanical and circulatory factors. *Am J Med* 1974;**57**:402–20.
7 Farebrother MJB. Respiratory function and cardiorespiratory response to exercise in obesity. *Br J Dis Chest* 1979;**73**: 211–25.
8 Luce JM. Respiratory complications of obesity. *Chest* 1980; **78**:626–31.
9 Naimark A, Cherniack RM. Compliance of the respiratory system and its components in health and obesity. *J Appl Physiol* 1960;**15**:377–82.
10 Suratt PM, Wilhoit SC, Hsiao HS, *et al*. Compliance of chest wall in obese subjects. *J Appl Physiol Respirat Environ Exerc Physiol* 1984;**57**:403–7.
11 Zerah F, Harf A, Perlemuter L, *et al*. Effects of obesity on respiratory resistance. *Chest* 1993;**103**:1470–6.
12 Leech JA, Onal E, Aronson R, *et al*. Voluntary hyperventilation in obesity hyperventilation. *Chest* 1991;**100**:1334–8.
13 Carrol D. A peculiar type of cardiopulmonary failure associated with obesity. *Am J Med* 1956;**21**:819–23.
14 Zwillich C, Sutton F, Pierson D, *et al*. Decreased hypoxic ventilatory drive in the obesity-hypoventilation syndrome. *Am J Med* 1975;**59**:343–8.
15 Cullen JH, Formel PF. The respiratory defects in extreme obesity. *Am J Med* 1962;**32**:525–31.
16 Pederson J, Torp-Pederson E. Ventilatory insufficiency in extreme obesity. *Acta Med Scand* 1960;**167**:343–8.
17 Sampson MG, Grassino A. Neuromechanical properties in obese patients during carbon dioxide rebreathing. *Am J Med* 1983;**75**:81–90.
18 Lopata M, Onal E. Mass loading, sleep apnea and the pathogenesis of obesity hypoventilation. *Am Rev Respir Dis* 1982;**126**:640–5.
19 Mountain R, Zwillich C, Weil J. Hypoventilation in obstructive lung disease. The role of familial factors. *N Engl J Med* 1978;**298**:521–5.
20 Fleetham JA, Arnup ME, Anthonisen NR. Familial aspects of ventilatory control in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1984;**129**:3–7.
21 Kawakami Y, Irie T, Kishi F, *et al*. Familial aggregation of abnormal ventilatory control and pulmonary function in chronic obstructive pulmonary disease. *Eur J Respir Dis* 1981;**62**:56–64.
22 Hudgel DW, Weil JV. Asthma associated with decreased hypoxic ventilatory drive. A familial study. *Ann Intern Med* 1974;**80**:622–5.
23 Read DJC. A clinical method for assessing the ventilatory response to CO_2. *Australas Ann Med* 1967;**16**:20.
24 Rebuck AS, Campbell EJM. A clinical method for assessing the ventilatory response to hypoxia. *Am Rev Respir Dis* 1974;**109**:345–50.
25 Weil JV, Byrne-Quinn E, Sodall IE, *et al*. Hypoxic drive in normal man. *J Clin Invest* 1970;**49**:1061–72.
26 Findley LJ. The close but mysterious ties between obstructive sleep apnea and the obesity-hypoventilation syndrome. *Chest* 1987;**92**:772–3.
27 Sullivan CE, Berthon-Jones M, Issa F. Remission of severe obesity hypoventilation syndrome after short term treatment during sleep with continuous positive airway pressure. *Am Rev Respir Dis* 1983;**128**:177–81.
28 Berthon-Jones M, Sullivan CE. Time course of change in ventilatory response to CO_2 in long-term CPAP treatment for obstructive sleep apnea. *Am Rev Respir Dis* 1987;**135**: 144–7.
29 Gold AR, Schwartz AR, Wise RA, *et al*. Pulmonary function and respiratory chemosensitivity in moderately obese patients with sleep apnea. *Chest* 1993;**103**:1325–9.
30 Piper AJ, Sullivan CE. Effects of short-term NIPPV in the treatment of patients with severe obstructive sleep apnea and hypercapnia. *Chest* 1994;**105**:434–40.
31 Hedemark LL, Kronenberg RS. Chemical regulation of respiration. *Chest* 1982;**82**:488–94.
32 Irsigler GB. Carbon dioxide response lines in young adults: the limits of the normal response. *Am Rev Respir Dis* 1976; **114**:529–36.
33 Hirshman CA, McCullough RE, Weil JV. Normal values for hypoxic and hypercapnic ventilatory drives in man. *J Appl Physiol* 1975;**38**:1095–8.
34 Arkinstall WW, Nirmel K, Klissouras V, *et al*. Genetic differencea in the ventilatory response to inhaled CO_2. *J Appl Physiol* 1974;**36**:6–11.
35 Collins DD, Scoggin CH, Zwillich CW, *et al*. Hereditary aspects of decreased hypoxic response. *J Clin Invest* 1978;**70**:105–10.
36 Kawakami Y, Yoshikawa T, Shida A, *et al*. Control of breathing in young twins. *J Appl Physiol* 1982;**52**:537–42.
37 Kawakami Y,Yamamoto H, Yoshikawa T, *et al*. Chemical and behavioral control of breathing in adult twins. *Am Rev Respir Dis* 1984;**129**:703–7.
38 Considine RV, Sinha MK, Heiman ML, *et al*. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *N Engl J Med* 1996;**334**:292–5.
39 Tankersley C, Kleeberger S, Russ B, *et al*. Modified control of breathing in genetically obese (ob/ob) mice. *J Appl Physiol* 1996;**81**:716–23.
40 Tankersley CG, O'Donnell C, Daood MJ, *et al*. Leptin attenuates respiratory complications associated with the obese phenotype. *J Appl Physiol* 1998;**85**:2261–9.
41 O'Donnell CP, Schaub CD, Haines AS, *et al*. Leptin prevents respiratory depression in obesity. *Am J Respir Crit Care Med* 1999;**159**:1477–84.
42 O'Donnell CP, Tankersley CG, Polotsky V. Leptin, obesity, and respiratory function. *Respir Physiol* 2000;**119**:163–70.
43 Kobayashi S, Nishimura M, Yamamoto M, *et al*. Dyspnea sensation and chemical control of breathing in adult twins. *Am Rev Respir Dis* 1993;**147**:1192–8.
44 Saunders NA, Heipern S, Rebuck AS. Relation between personality and ventilatory response to carbon dioxide in normal subjects: a role in asthma? *BMJ* 1972;1:718–21.
45 Hudgel DW, Kinsman RA. Interactions among behavioral style, ventilatory drive, and load recognition. *Am Rev Respir Dis* 1983;**128**:246–8.
46 Nishimura M, Yamamoto M, Yoshioka A, *et al*. Longitudinal analyses or respiratory chemosensitivity in normal subjects. *Am Rev Respir Dis* 1991;**143**:1278–81.
47 Kawakami Y, Yamamoto M,Yoshikawa T, *et al*. Respiratory chemosensitivity in smokers. *Am Rev Respir Dis* 1982;**126**: 986–90.
48 Leech JA, Onal E, Baer P, *et al*. Determinants of hypercapnia in occlusive sleep apnea syndrome. *Chest* 1987;**92**:807–13.
49 Ray CS, Sue DY, Bray G, Hansen JE, *et al*. Effects of obesity on respiratory function. *Am Rev Respir Dis* 1983;**128**:501–6.
50 Rapoport DM, Garay SM, Epstein H, *et al*. Hypercapnia in the obstructive sleep apnea syndrome. *Chest* 1986;**89**:627–35.
51 Lyons HA, Huang CT. Therapeutic use of progesterone in alveolar hypoventilation associated with obesity. *Am J Med* 1968;**44**:881–8.
52 Widdicombe JG. Nervous receptors in the respiratory tract and lungs. In: Hornbein TF, Lenfant C, eds. *Regulation of breathing. Part 1. Lung Biology in Health and Disease*. New York: Marcel Dekker, 1981:429–72.