Ventilatory responses to hypercapnia and hypoxia in patients with eucapnic morbid obesity before and after weight loss

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SUMMARY

1. To examine the relationship between eucapnic morbid obesity and ventilatory responsiveness to chemical stimuli, we measured hypercapnic and hypoxic ventilatory responses in 29 patients (26 women, three men) before and 3-6 months after gastroplasty. No subject demonstrated resting awake hypercapnia and none suffered from sleep-disordered breathing.

2. Mean weight fell significantly (122.8 ± 21.4 vs 102.2 ± 22.8 kg, P < 0.0001) and functional residual capacity rose slightly but significantly (1.94 ± 0.58 vs 2.18 ± 0.64 litres; P < 0.05) after weight loss.

3. The hypercapnic ventilatory response slope fell significantly after weight loss (2.88 ± 2.27 vs 2.24 ± 1.06 litres min⁻¹ mmHg⁻¹, P < 0.05) with a significant shift of the ventilatory response curve to the right. There were no statistically significant changes in the patterns of ventilatory response.

4. In addition, isocapnic hypoxic ventilatory response slopes, measured at two levels of carbon dioxide partial pressure, fell significantly after weight loss. These changes were accompanied by significant shifts of the ventilatory response curves to the left, such that, for a given oxygen saturation, mean ventilation was significantly lower in the less obese state. Similarly to hypercapnic responses, there were no statistically significant changes in ventilatory pattern despite the changes in overall ventilatory response.

5. We conclude that ventilatory responsiveness to chemical stimuli is increased in obese subjects who maintain adequate alveolar ventilation while awake.

Key words: control of breathing, hypercapnia, hypoxia, obesity, ventilation.

Abbreviations: fR, frequency of respiration; FEV₁, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; Paco₂, arterial partial pressure of carbon dioxide; Pco₂, partial pressure of carbon dioxide; Petco₂, end-tidal partial pressure of carbon dioxide; Pavco₂, mixed venous partial pressure of carbon dioxide; Sat₂, arterial oxygen saturation; Tᵣ, expiratory time, T₁, inspiratory time.

INTRODUCTION

The occasional association between obesity and impaired ventilatory drive is well-established. The relationship was first and most clearly seen in patients with the obesity-hypoventilation or 'Pickwickian' syndrome [1]. Later, the obstructive sleep apnoea syndrome was characterized and its link with obesity was noted [2]. Both disorders of ventilation are reported to improve after weight loss [1, 3, 4]. However, the effect of obesity on ventilatory drive has received comparatively little research attention, especially in the much larger group of subjects whose morbid obesity remains uncomplicated by respiratory failure.

A number of factors make it difficult to interpret conventional tests of ventilatory responsiveness in morbidly obese subjects. First, if respiratory failure is present, ventilatory response curves may be shifted in position simply by bicarbonate buffering. Treatment of the respiratory failure, whether by weight loss or other means, leads to shifting of the curves to a more 'normal' position, thereby complicating interpretation of any pre- and post-treatment comparison. Secondly, the effects of weight gain on ventilatory control mechanisms cannot necessarily be inferred by studies of weight loss if weight reduction is accompanied by profound metabolic changes. For example, dietary manipulation can lead to ketosis and increased responsiveness to inhaled carbon dioxide [5]; ileal bypass surgery can produce diarrhoea with accompanying acid–base shifts and, in extreme cases, malnutrition [6]. Thirdly, there is a wide range of normal values for measures of ventilatory responsiveness [7], so that comparison of obese subjects with a reference range or
normal population will be an insensitive means of detecting obesity-induced alterations of the ventilatory control system. For these reasons, we undertook the following prospective study to examine ventilatory responses to progressive hyperoxic hypercapnia and to progressive isocapnic hypoxia in a relatively large population of patients with eucapnic morbid obesity undergoing gastroplasty to induce weight loss. Patients were studied if they did not suffer from respiratory failure and weight loss was achieved gradually yet reliably in a relatively short time without metabolic complications. Finally, each patient served as his or her own control in the assessment of the effects of obesity on ventilatory responsiveness.

METHODS

Patients

Between October 1984 and May 1988, all patients considered for gastroplasty in the treatment of morbid obesity were assessed by a member of the Respiratory Division. Those meeting inclusion and exclusion criteria for the trial underwent pulmonary function testing including measurement of ventilatory responses to hypercapnia and hypoxia before and again 3–6 months after gastroplasty.

Gastroplasty was performed as previously described [8] and was accompanied by appropriate dietary counselling. The protocol was approved by the Human Subjects Review Committee of the University of Toronto and written, informed consent was obtained from all patients.

Patients with a history of chronic respiratory disease or significant non-respiratory medical illnesses were excluded from the trial, as were those in whom spirometry revealed significant airflow limitation [forced expiratory volume in 1 s/forced vital capacity (FEV₁/FVC) ratio ≤70%]. Those with a known or suspected diagnosis of obstructive sleep apnoea were excluded from the analysis and those reporting symptoms suggestive of this disorder underwent overnight oximetry, polysomnography or both, to exclude the diagnosis. Patients with a resting arterial partial pressure of carbon dioxide (Paco₂) of ≥45 mmHg (5.99 kPa) while awake were not studied. Data from patients who fail to achieve a 10 kg or greater weight loss after surgery were not analysed.

Procedures

Resting pulmonary mechanics were measured in the Pulmonary Function Laboratory on the day before rebreathing procedures were performed. Flow–volume spirometry was performed with the patient in the sitting posture and the best of at least three maximal curves was chosen according to the American Thoracic Society guidelines [9]. Functional residual capacity (FRC) was measured by helium dilution and diffusion capacity by the single-breath carbon monoxide method. Arterial blood was sampled by radial artery puncture as the patient sat quietly at rest, breathing room air.

On the day of the rebreath studies, patients were asked to abstain from coffee, tea and xanthine-containing beverages. The ventilatory response to progressive hyperoxic hypercapnia was measured by the Read method using a bag-in-box rebreathe circuit as previously described [7, 10]. The ventilatory response to progressive isocapnic hypoxia was measured by the Re buck–Campbell method at two partial pressures of carbon dioxide (Pco₂), one approximating the subject’s resting end-tidal partial pressure of carbon dioxide (Petco₂) and one approximating his or her oxygenated mixed venous partial pressure of carbon dioxide (Pvco₂) [7, 11]. One of two different transmittance oximeters were used to monitor arterial oxygen saturation (Sao₂) continuously (Hewlett-Packard HP47201A or Biox III), but care was taken that the same instrument was used before and after surgery for each individual [12, 13]. Analog output from these devices was digitized via an analog to digital converter at 20 Hz and the resulting data were stored on diskette for subsequent analysis. These data were analysed using breath detection software developed by the University of Toronto Medical Computing Group, allowing breath by breath qualification of inspiratory time (T₁), expiratory time (Tₑ), tidal volume (V₁), Petco₂ and Sao₂, and breath by breath calculation of regression slopes.

Data analysis

Ideal body weight was derived from standard tables [14]. Results are expressed as means ± s. Pre- and postoperative variables were compared by using a paired t-test, except for response slopes which were compared using the Wilcoxon signed rank test to account for their non-normal distribution. Differences were considered significant at the P < 0.05 level. When significant postoperative changes were detected, correlations between degree of weight loss and change in ventilatory response were sought using least squares linear regression.

RESULTS

Physical characteristics and pulmonary function

Forty-one patients (12 men, 29 women) underwent gastroplasty and were referred for respiratory assessment during the study period. Twelve of these patients were excluded from the study because of a diagnosis of sleep apnoea made polysomnographically either previously or at the time of pre-operative assessment. Of the remaining 29 patients, 18 underwent overnight oximetry and four underwent polysomnography for evaluation of snoring or non-refreshing sleep. In none of these patients was significant desaturation or sleep apnoea found. These patients free of respiratory complications of obesity (three men, 26 women) were studied in greater detail pre- and post-operatively. Their mean age was 40.5 ± 9.5 years and mean weight before surgery was 122.8 ± 21.4 kg or 223 ± 41.5% of ideal body weight. Before surgery, the mean pH was 7.42 ± 0.03, mean Paco₂ was 39.7 ± 4.55 mmHg (5.28 ± 0.61 kPa), mean Pao₂ was 79.2 ± 8.61 mmHg (10.5 ± 1.15 kPa) and mean plasma bicarbonate
Post-operative arterial puncture was not performed routinely in all patients and too few data are available for meaningful comparison with pre-operative values. Mean (±sd) values of anthropomorphic and pulmonary function variables are given in Table 1. Weight fell significantly by 20.6±9.6 kg or 17.2% of pre-operative weight. Similarly, body surface area fell significantly after surgery. FRC rose significantly, the mean increase being 0.19±0.36 litre or 10.7% of predicted. Changes in other variables were not statistically significant.

Ventilatory responsiveness to carbon dioxide

The oxygenated PCO2 derived from the equilibration plateau of the Read rebreathe was 48.8±4.3 mmHg (6.49±0.57 kPa) before surgery and fell to 46.8±3.4 mmHg (6.22±0.45 kPa) after surgery (P<0.01). A PCO2 equilibration plateau was also recorded during hypoxic rebreathing studies performed at PCO2 levels; the oxygenated PCO2 derived from these studies also fell, by 2.1±4.3 mmHg (0.28±0.57 kPa) (P<0.05). Hypercapnic ventilatory response slopes fell significantly after surgery (2.88±2.27 vs 2.24±1.06 litres min⁻¹ mmHg⁻¹; P<0.05; Fig. 1).

The carbon dioxide response curve was shifted to the right after surgery such that mean ventilation at a PCO2 of 55 mmHg (7.32 kPa) was significantly lower (see Table 2). There were no statistically significant differences in the pattern of hypercapnic ventilatory response expressed as the slopes of VT, frequency of respiration (fR) or T1 versus PCO2 (see Table 2). After surgery there was a non-significant trend toward a lower frequency response slope.

There was no significant linear correlation between amount of weight loss and the change in hypercapnic ventilatory response slope. When hypercapnic ventilatory response slopes were corrected for body size by dividing by body surface area, the post-operative decrease was no longer statistically significant (1.32±1.10 vs 1.08±0.53 litres min⁻¹ mmHg⁻¹ m⁻²; P>0.1).

Ventilatory responsiveness to hypoxia

Both hypoxic ventilatory response slopes fell significantly after surgery (see Fig. 1). The isocapnic PCO2 level of the hypoxic test performed at resting PETCO2 levels did not differ significantly before and after surgery [37.6±2.83 mmHg (5.00±0.38 kPa) vs 37.1±4.9 mmHg (4.93±0.65 kPa), respectively; P>0.2]. Pre- and post-operative ventilatory response slopes were 1.05±0.67 litres min⁻¹ (% fall in SaO2)⁻¹ and 0.80±0.64 litre min⁻¹ (% fall in SaO2)⁻¹, respectively (P<0.05). By contrast, the isocapnic PCO2 levels of the hypoxic test performed at higher levels of PETCO2 was significantly lower after surgery [47.7±4.1 mmHg (6.34±0.55 kPa) vs 45.5±3.9 mmHg (6.05±0.52 kPa), respectively; P<0.05]. Pre- and post-operative hypoxic response slopes at these PCO2 levels were 1.80±1.37 litres min⁻¹ (% fall in SaO2)⁻¹ and 1.41±0.69 litres min⁻¹ (% fall in SaO2)⁻¹, respectively, P<0.05. The interactive effect of hypercapnia and hypoxia, quantified as the a1 parameter of Rebuck & Slutsky [7], was not changed after surgery [0.08±0.12 before surgery vs 0.09±0.08 litre min⁻¹ (% fall in SaO2)⁻¹ after surgery; P>0.20]. Both hypoxic ventilatory response slopes shifted significantly to the left such that for a given saturation, mean ventilation was significantly lower after surgery. When PCO2 approximated normal PETCO2 levels and SaO2 was reduced to 80%, mean ventilation was 30.2±12.1 litres/min before but was 25.3±12.4 after surgery (P<0.05). When PCO2 levels approximated those of PETCO2 during hypoxic testing, mean ventilation before and after surgery was 56.0±26.5 litres/min and 45.9±15.2 litres/min, respectively (P<0.05), when SaO2 was 80%. There were no significant differences in the ventilatory patterns of hypoxic response before and after surgery when examined as the VTfR and T1 response slopes.

As for hypercapnic ventilatory response slopes, there was no significant linear relationship between amount of weight loss and the change in hypoxic slopes. When hypoxic ventilatory slopes were corrected for body size by dividing by body surface area, the decreases after surgery were no longer statistically significant. For hypoxic tests performed at PETCO2 of 37 mmHg (4.92 kPa), pre- and post-operative values were 0.47±0.29 vs 0.38±0.28 litre min⁻¹ (% fall in SaO2)⁻¹ (P=0.07); for hypoxic tests done at 46 mmHg (6.1 kPa), corresponding values were 0.80±0.58 vs 0.69±0.32 litre min⁻¹ (% fall in SaO2)⁻¹ (P>0.1).

DISCUSSION

In a large group of patients with eucapnic morbid obesity, we have shown that weight loss after gastroplasty is accompanied by significant reductions in hypercapnic and hypoxic ventilatory response slopes. These changes occurred in the face of modest weight loss, minimal

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Body surface area (m²)</th>
<th>FVC (litres)</th>
<th>FEV₁ (litres)</th>
<th>FRC (litres)</th>
<th>RV (litres)</th>
<th>DLco (% of predicted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before surgery</td>
<td>122.8±21.4</td>
<td>2.16±0.41</td>
<td>3.58±0.85</td>
<td>3.00±0.67</td>
<td>1.94±0.58</td>
<td>1.36±0.58</td>
</tr>
<tr>
<td>After surgery</td>
<td>102.2±22.8 †</td>
<td>1.99±0.39 †</td>
<td>3.63±0.90</td>
<td>2.99±0.75</td>
<td>2.18±0.64 *</td>
<td>1.36±0.44</td>
</tr>
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</table>

*P<0.05, †P<0.0001 compared with before surgery.
changes in conventional measures of pulmonary function and without significant changes in the component patterns of the ventilatory response.

Our findings suggest that ventilatory responsiveness to chemical stimuli is enhanced in obese subjects who maintain adequate alveolar ventilation while awake. The inference is compatible with, and extends the observations of, some studies that have compared obese but normocapnic subjects with healthy volunteers or with patients with the obesity-hypoventilation syndrome. In an early study of eucapnic morbid obesity, Emirgil & Sobol [15] used steady-state tests to show that carbon dioxide responsiveness fell in four obese subjects after weight loss. Later studies by Gilbert et al. [16] and Kronenberg et al. [17] failed to confirm this finding, but their study populations were not limited to uncomplicated eucapnic obesity. Burki & Baker [18], measuring hypercapnic and hypoxic ventilatory responses in 14 eucapnic obese subjects and 11 normal volunteers, were able to identify augmented hypoxic response slopes in the obese subjects but could find no difference in hypercapnic slopes. Their results must be interpreted cautiously, as they chose to derive a single hypercapnic response slope by pooling the rebreathe data from all subjects in the group. In this pooling of data, each obese subject contributed less than three data points to the 'mean' slope for the obese group, whereas each normal volunteer contributed almost eight points to their group's 'mean' slope. More importantly, 70% of the obese subjects studied were female yet all control subjects were male.

Ventilatory responses to hypercapnia and hypoxia are preserved in normal volunteers subjected to elastic loading or to loading of the diaphragm achieved by adoption of the supine posture [19-22]. Lopata & Onal [2] have shown that mass loading of the abdomen in normal subjects leads to enhanced electromyographic, occlusion pressure and ventilatory responses to inhaled carbon dioxide. Similar compensatory mechanisms, presumably neural, were probably at work in our obese subjects. However, large changes in mechanical loads are usually marked by alteration in ventilatory pattern, yet we found no consistent pattern changes as our subjects lost weight. A non-mechanical and non-neural explanation for our findings is the change in resting metabolic rate that results from weight loss or weight gain; increased metabolic rate augments the hypoxic ventilatory response [23]. Although we did not measure metabolic rate directly, it is reasonable to assume that metabolic rate was higher in our patients before surgery. To the extent that body surface area reflects metabolic rate, our data offer some indirect evidence that changes in metabolic rate were related to the observed changes in ventilatory response slopes; when corrected for body surface area, ventilatory slopes were no longer significantly different before and after weight loss. We did not find a significant linear relationship between the amount of weight loss and the change in ventilatory slopes, although there were non-significant trends, such that patients showing the greatest weight loss were likely to show the greatest changes in response slopes. The lack of significance in this relationship may suggest that the sample size was too small to demonstrate such a relationship or that the relationship is not a simple linear one. It is noteworthy that the post-operative decrease in ventilation at a PCO₂ of 55 mmHg during hypercapnic responses and the decrease in ventilation at an SÅO₂ of 80% during hypoxic responses, were similar in percentage terms to the decrease in body weight.

Hormonal factors may have contributed to the changes we observed. Large adipose mass is associated with both increased oestrogen storage and increased conversion of adrenal androgens to oestrone [24]. A recent study has shown that oestrone works synergistically or additively with other metabolic stimuli to augment hypoxic ventilatory responsiveness [25]. As well, cyclical changes in

Table 2. Pattern of hypercapnic ventilatory responses before and after surgery

<table>
<thead>
<tr>
<th></th>
<th>Ventilation (litres/min) at PCO₂ = 55 mmHg (7.32 kPa)</th>
<th>V₁ response slope (litre/mmHg)</th>
<th>f₁ response slope (breaths min⁻¹ mmHg)</th>
<th>T₁ response slope (s/mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before surgery</td>
<td>34.3 ± 20.4</td>
<td>0.080 ± 0.07</td>
<td>0.74 ± 0.74</td>
<td>−0.025 ± 0.031</td>
</tr>
<tr>
<td>After surgery</td>
<td>27.2 ± 11.5*</td>
<td>0.075 ± 0.03</td>
<td>0.50 ± 0.35</td>
<td>−0.022 ± 0.029</td>
</tr>
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progestrone levels are known to alter ventilatory responsiveness in pre-menopausal women. In the present ventilatory study, ventilatory measurements were performed at random times during the menstrual cycle, a study design likely to increase the background variability of ventilatory response tests but minimizing the possibility of systematic bias with respect to progestrone levels. Because the majority of our patients were women and most were pre-menopausal, our findings of enhanced ventilatory responsiveness to chemical stimuli may not be applicable to the obese of both sexes. However, Kunitomo et al. [26] have found greater hypoxic ventilatory response slopes among male and female normoecapnic obese subjects when compared with sex-matched non-obese controls subjects. In their study, hypocapnic ventilatory response slopes were higher in obese than in normal subjects, although this trend was not statistically significantly for their small group of obese male subjects.

Although rebreathing studies of ventilatory control are generally regarded as offering results comparable with those of steady-state tests, we cannot rule out the possibility that some or all of the change in ventilatory slopes was consequence of rebreathing techniques we employed. For example, starting Pco2 levels, FRC and cardiac output may all have independent effects on rebreathe slopes for carbon dioxide [27]. In this study, FRC rose slightly between measurements, a change which would tend to lower rebreathe slopes. It is also likely that cardiac output fell after surgery with the decrease in body mass. We have not reported post-operative Paco2 values; arterial puncture was performed for clinical purposes before surgery but was felt to be inappropriately invasive for purely research purposes after surgery. Oxygenated Paco2 and Petco2 were measured and showed minimal decreases after surgery. It is therefore likely that Paco2 values fell slightly with weight loss.

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REFERENCES