SUMMARY

Two obese patients with acute respiratory failure are described. Both required mechanical ventilation to reverse the respiratory acidosis. On recovery, the major abnormality was failure of ventilatory response to inhaled carbon dioxide. After oral progesterone (100 mg/day and 20 mg/day, respectively) the slope of the carbon dioxide response line increased from 0.02 to 1.14 l/min⁻¹ mmHg⁻¹ and from 0.04 to 1.14 l/min⁻¹ mmHg⁻¹ respectively. This was associated with sustained clinical remission in 1 patient.


Patients with the syndrome of obesity, heart failure, and hyperventilation have been the subject of many reports. They present difficult problems in management and the mortality is high. The pathogenesis of hyperventilation in these patients may be related to inadequate chemoreceptor drive to respiration. Progesterone has been used in the treatment of ambulatory patients because of its stimulant effect on ventilation. This report describes the successful use of progesterone to restore carbon dioxide responsiveness in 2 obese patients with respiratory failure, with maintained long-term remission in 1.

CASE REPORT

Patient 1

A 53-year-old mentally retarded woman was admitted to hospital in respiratory failure (Pco₂ 71 mmHg) (Table I). For the previous 7 months, since having caught a cold, she had complained of persistent coughing, a weight gain of 9 kg and progressive dyspnoea on effort. She was admitted because of worsening dyspnoea for 2 days. On examination she was obese (weight 86.4 kg, height 155 cm) and lethargic, with cyanosis. The respiration was 20/min and pulse and blood pressure were normal. Breath sounds were uniformly decreased with crepitations at both lung bases. Other findings included erythrocytosis (Hb 19.6 g/dl, haematocrit 60%), normal serum urea and electrolyte levels and normal thyroid function studies. The chest radiograph showed cardiomegaly and pulmonary oedema.

The ECG showed clockwise rotation in precordial leads with low voltage in S1 - S3. The vital capacity (VC) was 1.5 l (54% of predicted value). Because she was awake and co-operative, it was decided to treat her with digoxin, furosemide, aminophylline, and low-flow oxygen. On the 8th day, after an episode of haemoptysis, a lung scintiscan revealed a large perfusion defect in the left lower lobe. Pulmonary function tests were not done at this time.

Intravenous heparin infusion was begun. Apnoea was not observed during sleep at any time. By the 26th day she had lost 7.3 kg. Four days later she required mechanical ventilation because of rapidly worsening hyperventilation (Pco₂ 127 mmHg, 17 April 1975, Table I). She was sedated with morphine 5 mg and pancuronium 6 - 10 mg intravenously every 4 hours as needed. Weaning was begun on the 4th day after intubation. The last sedation was given at 18h00 on 21 April and she was extubated at 12h00 on the following day after having breathed unassisted for 6 hours. Arterial blood taken immediately before extubation showed mild metabolic alkalosis and hypercapnia (base excess +5.0, Pco₂ 45 mmHg, 22 April, Table I). A rebreathing test later that day showed absence of response in ventilation as end-tidal Pco₂ increased from 54 to 61 mmHg (Table I, Fig. 1). Progesterone treatment (dydrogesterone 50 mg twice a day) was begun. After 5 weeks she was eucapnic and weighed 76 kg, but her VC had improved marginally (1.65 litre). Complete spirometric evaluation was impossible due to the patient's intellectual impairment. There was a striking change in her response to carbon dioxide (2 June, Table I, Fig. 1). After 1 year dydrogesterone had been reduced to 15 mg daily, she weighed 66.3 kg, and her VC was 1.9 litre (62% of pre-

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Date received: 6 October 1978.

Fig. 1. CO₂ response lines in patient 1, relating ventilation to end-tidal Pco₂. Individual points represent measurements at half-minute intervals before progesterone (closed circles), and after progesterone (open circles), i.e. the first data point in each test is taken at 1 minute of rebreathing. The line of best fit was obtained by least squares regression of V̇E on Pco₂. The equations for the regression lines are: y = 0.03 x + 6.21 (22 April 1975); y = 1.14 x — 42.7 (2 June 1975).
dicted value). Arterial blood gases showed a compensated respiratory acidosis (Table I). The haemoglobin level was 16.1 g/dl. The carbon dioxide response was intermediate to that in the previous two studies (Table I).

![Graph showing CO₂ response lines in patient 2. Points represent measurements at 15-second intervals, after the first half minute of rebreathing has elapsed. Symbols as in Fig. 1. Regression lines are $y = 0.04 \times 24.1$ (26 May 1977); $y = 1.14 x - 35.8$ (2 June 1977).](image)

**Patient 2**

A 46-year-old obese female nurse was admitted to hospital in respiratory failure (Pco₂ 85 mmHg) (Table I). She had gained weight for the past 5 years, had been treated for cardiac failure and hypertension for the past year, and had become increasingly somnolent during the preceding 2 months. On the morning of admission she had become semicomatose. On examination she was obtunded and deeply cyanosed. Her weight was 125.5 kg and her height 170 cm. Pulse and blood pressure were normal, and respiratory rate was 35/min. Auscultation revealed decreased air entry with crepitations at both lung bases. She had erythrocytosis (Hb 19.5 g/dl, haematocrit 58%) and normal serum urea, electrolytes, thyroxine and free thyroxine index. A chest radiograph showed cardiomegaly. There were no pulmonary infiltrates. The ECG showed a vertical QRS axis and P pulmonale. She was treated initially with phlebotomy, aminophylline, furosemide, digitalis, penicillin, heparin and mechanical ventilation for 3 days, with good response (23 May 1977, Table I). While on the respirator she was sedated with diazepam 10 mg and pancuronium 4-6 mg intravenously. The last dose of each drug was given at midnight on 21 May. By the 6th day she was walking about the ward and slept without apnoea through the night. Her VC was 2.75 l (77% of predicted value), total lung capacity (TLC) 5.30 l (98%), FEV₁ 2.0 l (73%), and maximal voluntary ventilation (MVV) 60 l/min. The maximal expiratory flow volume curve showed a peak flow (PF) of 6.8 l/s, flow with 50% VC remaining (V₅₀) 1.8 l/s, and flow with 25% VC remaining (V₅₅) 0.8 l/s.

Airways resistance (Rₐw), measured at functional residual capacity during tidal breathing in a constant volume body box, was 2.9 cm H₂O l⁻¹ s⁻¹. The arterial pH and Pco₂ were normal. However, there was no ventilatory response to CO₂ (26 May, Table I, Fig. 2). Dydrogesterone 20 mg per day was begun, and treatment was continued with digoxin, diuretics and a 3000-kJ diet. Seven days later there was no marked change in pulmonary function: VC 2.55 l, TLC 5.17 l, FEV₁ 1.8 l (71%), and MVV 58 l/min. PF was 6.6 l/s, V₅₀ 1.9 l/s, V₅₅ 0.8 l/s, and Rₐw 5.74 cm l⁻¹ s⁻¹. There was a striking change in the ventilatory response to CO₂ (Fig. 2, Table I).

### Table I. Arterial Blood Gas Values and CO₂ Response

<table>
<thead>
<tr>
<th>Date</th>
<th>Treatment</th>
<th>P₀₂ (mmHg)*</th>
<th>pH*</th>
<th>P₁₀₂ (mmHg)*</th>
<th>HCO₃⁻ (mM/l)*</th>
<th>Base excess</th>
<th>S</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>On admission</td>
<td>43</td>
<td>7.29</td>
<td>71</td>
<td>33.5</td>
<td>+7.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 March 1975</td>
<td>Conservative (before intubation)</td>
<td>31</td>
<td>7.10</td>
<td>127</td>
<td>38.5</td>
<td>+8.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17 April 1975</td>
<td>Before extubation (F₁₂O₂ 0.8)</td>
<td>60</td>
<td>7.43</td>
<td>45</td>
<td>29.7</td>
<td>+5.0</td>
<td>0.02</td>
<td>-330</td>
</tr>
<tr>
<td>22 April 1975</td>
<td>Dydrogesterone 100 mg/d</td>
<td>50</td>
<td>7.36</td>
<td>42</td>
<td>23.5</td>
<td>-1.5</td>
<td>1.14</td>
<td>37.1</td>
</tr>
<tr>
<td>21 May 1975</td>
<td>Dydrogesterone 100 mg/d</td>
<td>64</td>
<td>7.39</td>
<td>52</td>
<td>31</td>
<td>+5</td>
<td>0.27</td>
<td>29.4</td>
</tr>
<tr>
<td>29 March 1976</td>
<td>Dydrogesterone 15 mg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

* Normal for Pretoria (1336 m altitude): P₀₂ 75 ± 5 mmHg, P₁₂O₂ 36 ± 2 mmHg, H₁₂O 22 - 27 mM/l. All values in room air unless otherwise stated.

† Extracellular fluid base excess, 5 g Hb line.

S = slope of the $V_{E}$-P₁₂O₂ response line (I min⁻¹ mmHg⁻¹); B = intercept of the response line on the P₁₂O₂ axis (mmHg).

Fig. 2. CO₂ response lines in patient 2. Points represent measurements at 15-second intervals, after the first half minute of rebreathing has elapsed. Symbols as in Fig. 1. Regression lines are $y = 0.04 \times 24.1$ (26 May 1977); $y = 1.14 x - 35.8$ (2 June 1977).
Carbon Dioxide Response Testing

The ventilatory response to carbon dioxide was determined by a non-steady state technique modified after Read. A detailed description of the method we used has appeared elsewhere. A Stead Wells spirometer was filled to a volume of 6 litres with a gas mixture containing 6 - 6.5% CO₂, 60% O₂, balance N₂, except in the 1-year follow-up study of patient 1, when 7.0% CO₂ was used. End-tidal CO₂ was measured continuously at the mouth (infrared CO₂ analyser; Capnograph, Godart). Ventilation was calculated from half-minute segments of the kymograph tracing from the spirometer (patient 1), or by integration of inspiratory flow measured by a heated pneumotachograph at the mouth (Godart Model 17212) (patient 2). The CO₂ response line was obtained by plotting corresponding values of ventilation against end-tidal PCO₂. The relationship of ventilation to PCO₂ is given by VE = S(PCO₂ - B), where Vₑ is the minute volume of ventilation, S is the slope of the CO₂ response line, and B is the PCO₂ when Vₑ equals 0, i.e. the intercept of the response line on the PCO₂ axis. S is an estimate of the sensitivity of the central chemoreceptors, and B is thought to be related to the CO₂ threshold. Eighty per cent of a series of normal subjects studied in this way had an S value of between 1.5 and 5.0 1 min⁻¹ mmHg⁻¹. Others have found the normal range for S to be 1.00 - 5.95 1 min⁻¹ mmHg⁻¹.

DISCUSSION

Alveolar hypoventilation probably occurs in less than 10% of very obese patients. Why some hypoventilate while others, also overweight, do not, has been much discussed. One unresolved question is whether the primary defect is an intolerable increase in the work of breathing due to body mass, or whether the disease is one of disordered respiratory control. Whereas compliance of both the lung and the chest wall are more reduced in patients who hypoventilate, it has been shown that impairment of carbon dioxide responsiveness is unrelated to body mass. There is also blunting of sensitivity to hypoxia. In other obese patients, hypoventilation results from intermittent obstruction of the upper airways during sleep; this is relieved by tracheostomy and is not necessarily related to an impaired chemoreceptor drive. Clearly, more than one pathogenetic mechanism for this clinical syndrome may exist. Since the mortality from respiratory failure in obesity is still high, it is important to establish precisely the mechanisms involved to facilitate appropriate clinical management.

Progesterone has been used with some success to treat hypoventilation in obesity. The site and mechanism of action and optimal dose are unknown. Augmentation of ventilation occurs within 24 hours.

Our patients presented with the well-known features of hypoventilation associated with obesity: hypoxaemia with resultant erythrocytosis; and hypercapnia and respiratory acidosis, together with hypoxaemia, leading to drowsiness and congestive cardiac failure. On recovery, the major abnormality was failure of ventilatory response to inhaled CO₂. Neither patient had evidence of pulmonary disease that could explain the hypoventilation, and in both patients CO₂ responsiveness was restored after treatment with progesterone. However, this effect may not be sustained, as shown by the recurrence of CO₂ insensitivity in patient 1 after 1 year.

The question arises whether other physiological, pharmacological or metabolic effects could account for the improvement in CO₂ responsiveness which we observed. One consideration is a change in elastic or resistive loading during the course of treatment, which would influence the ventilatory response to CO₂. Pulmonary function testing was difficult in patient 1, owing to her intellectual impairment. However the VC, an indirect measure of elastic loading, did not change appreciably between the first and the follow-up test. In patient 2, VC and static lung volumes remained essentially unaltered. Resistive loading was assessed by measurement of Rmin and maximal expiratory flow rates. Rmin was higher during treatment with progesterone, and expiratory flow rates were the same. We conclude that changes in mechanical properties of the lungs and chest wall during treatment did not contribute to the improved response to CO₂ which we observed.

Respiratory suppressant drugs had been discontinued for 20 hours (patient 1) and 6 days (patient 2) before the CO₂ response tests, and neither patient had evidence of myxoedema.

Respiratory failure in obesity requires early and active intervention, which should include treatment of precipitating factors, e.g. respiratory infection, and aggressive treatment of cardiac failure. Later, an accurate aetiological diagnosis should be established by screening tests of pulmonary function, examination of upper airways and electro-encephalographic monitoring during sleep. This report indicates that a test of ventilatory response to CO₂ or hypoxia should also be performed. If this is abnormal and hypoventilation persists, progesterone should be given in the initial phase of management, while measures aimed at weight reduction take effect.

REFERENCES