VENTILATORY RESPONSE TO EXERCISE AND TO CO₂ REBREATHEING IN NORMAL SUBJECTS

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SUMMARY

1. Changes in ventilation during progressive exercise were measured in eleven normal subjects. Ventilatory response to carbon dioxide at rest was measured in the same subjects using a rebreathing method.

2. The range of ventilatory response to exercise was 16.6-32.0 litres min⁻¹ (litres CO₂ min⁻¹)⁻¹ (mean 22.7; SD 5.35); response to O₂ uptake was 17.0-43.9 litres min⁻¹ (litres O₂ min⁻¹)⁻¹ (mean 29.02; SD 9.07). Ventilatory response to CO₂ (Sco₂) ranged from 0.81 to 3.22 litre min⁻¹ mmHg⁻¹ (mean 1.87; SD 0.62).

3. There was a highly significant (P<0.001) correlation between the changes in response to increasing CO₂ output or O₂ uptake, and Sco₂.

4. The results are compatible with the suggestion that ventilation during exercise in normal subjects is directly related to their chemosensitivity to CO₂, those having the highest sensitivity showing the greatest exercise ventilation.

Key words: CO₂ response, ventilation, exercise.

The ventilatory response to CO₂ varies greatly between subjects (Rebuck & Read, 1971; Godfrey, Edwards, Copland & Gross, 1971), and we have also noticed the variability between subjects in ventilatory response to exercise during clinical exercise tests. In the present study we examine the relation between ventilatory response to CO₂ and ventilatory response to exercise in a group of normal subjects.

SUBJECTS AND METHODS

Ventilatory response to exercise was recorded using stepwise increases in power on a cycle ergometer. Ventilatory response to CO₂ was recorded by Read's (1967) rebreathing technique.

The subjects were eleven members of the department medical and technical staff. All were leading an active life, but none was in athletic training, and details are given in Table 1.

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<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>FEV$_{1.0}$ (L)</th>
<th>$V_{O2}$ max (ml/min)</th>
<th>Upper level of linear ventilatory response</th>
<th>Exercise</th>
<th>Rest</th>
</tr>
</thead>
<tbody>
<tr>
<td>R.C.</td>
<td>31</td>
<td>F</td>
<td>157.5</td>
<td>39.5</td>
<td>2.80</td>
<td>1500</td>
<td>500</td>
<td>32.0</td>
<td>43.9</td>
</tr>
<tr>
<td>N.J.</td>
<td>40</td>
<td>M</td>
<td>189.2</td>
<td>96.0</td>
<td>4.50</td>
<td>3750</td>
<td>1200</td>
<td>24.5</td>
<td>30.2</td>
</tr>
<tr>
<td>T.L.</td>
<td>29</td>
<td>M</td>
<td>167.6</td>
<td>58.6</td>
<td>3.40</td>
<td>2150</td>
<td>800</td>
<td>22.1</td>
<td>32.2</td>
</tr>
<tr>
<td>D.M.</td>
<td>30</td>
<td>M</td>
<td>184.2</td>
<td>80.9</td>
<td>3.85</td>
<td>3250</td>
<td>1000</td>
<td>16.6</td>
<td>17.0</td>
</tr>
<tr>
<td>M.M.</td>
<td>27</td>
<td>F</td>
<td>165.1</td>
<td>80.5</td>
<td>3.50</td>
<td>2600</td>
<td>1000</td>
<td>17.0</td>
<td>17.4</td>
</tr>
<tr>
<td>L.P.</td>
<td>29</td>
<td>F</td>
<td>162.6</td>
<td>55.0</td>
<td>2.80</td>
<td>1925</td>
<td>700</td>
<td>21.4</td>
<td>29.5</td>
</tr>
<tr>
<td>A.S.</td>
<td>34</td>
<td>M</td>
<td>185.4</td>
<td>89.1</td>
<td>3.95</td>
<td>3040</td>
<td>1200</td>
<td>23.9</td>
<td>25.5</td>
</tr>
<tr>
<td>D.R.</td>
<td>35</td>
<td>M</td>
<td>166.4</td>
<td>68.2</td>
<td>3.33</td>
<td>2900</td>
<td>900</td>
<td>17.3</td>
<td>22.6</td>
</tr>
<tr>
<td>M.S.</td>
<td>30</td>
<td>M</td>
<td>176.6</td>
<td>75.5</td>
<td>4.95</td>
<td>3250</td>
<td>1100</td>
<td>18.9</td>
<td>23.2</td>
</tr>
<tr>
<td>J.T.</td>
<td>26</td>
<td>F</td>
<td>165.1</td>
<td>59.1</td>
<td>3.35</td>
<td>1902</td>
<td>700</td>
<td>25.0</td>
<td>35.0</td>
</tr>
<tr>
<td>G.V.</td>
<td>33</td>
<td>M</td>
<td>172.7</td>
<td>70.9</td>
<td>3.65</td>
<td>2650</td>
<td>900</td>
<td>31.3</td>
<td>42.7</td>
</tr>
</tbody>
</table>

$\Delta V_{E}/\Delta V_{CO2}$ = litres min$^{-1}$ (litres CO$_2$ min$^{-1}$)$^{-1}$ during exercise.
$\Delta V_{E}/\Delta V_{O2}$ = litres min$^{-1}$ (litres O$_2$ min$^{-1}$)$^{-1}$ during exercise.
$\Delta V_{E}/P_{CO2}$ = ventilatory response to CO$_2$ (litres min$^{-1}$ mmHg$^{-1}$).
$V_{O2}$ max = maximal oxygen uptake (ml/min) achieved at the maximal power.
The upper level of linear ventilatory response is the work load below which the ventilatory response to exercise was used to obtain $\Delta V_{E}/\Delta V_{CO2}$ and $\Delta V_{E}/\Delta V_{O2}$. 
Ventilation in exercise

subjects all gave their informed consent to the procedure, but were not informed about the results of any studies until they had been completed.

Exercise measurements were made with an electrically braked cycle ergometer (Elema). A low dead-space mouthpiece was connected through a Lloyd valve, with a combined dead-space of 56 ml. Expired gas passed through a mixing chamber (6 litres), and inspired ventilation was measured with an accuracy of ±1% by a Parkinson–Cowan CD4 dry-gas meter fitted with a potentiometer connected to the output shaft. The inspiratory resistance of the circuit was 1.8 cmH₂O at a flow rate of 3.0 litres/s and on expiration was 0.9 cmH₂O at this flow rate. Gas was continually sampled at the outlet of the mixing chamber, and was analysed by an infra-red CO₂ analyser (Capnograph, Godart), accurate to ±0.1% over the range 0–8%, and by a paramagnetic O₂ analyser (Servomex), with an accuracy of ±0.1%. Both analysers were calibrated before each study using several gas mixtures which had previously been analysed in the Lloyd–Haldane apparatus. The analysers were used to measure mixed expired O₂, CO₂ and end-tidal PCO₂. Measurements of ventilation, frequency of breathing, tidal volume, CO₂ output, O₂ uptake, and respiratory exchange ratio were calculated by online computer (PDP8–1) which was working in real time. Results were displayed every 20 s during the procedure.

Ventilatory response to CO₂ was measured using a bag (6 litres) containing an initial gas mixture of CO₂ + O₂ (7 : 93). The rebreathing bag was enclosed in an airtight glass container which was connected to the dry-gas meter fitted with a potentiometer, allowing ventilation during rebreathing to be recorded on a direct-writing recorder (Mingograf 81). A continuous record of CO₂ concentration in the expired gas was obtained by drawing a sample of gas from the mouthpiece through the Capnograph; the sample was returned to the rebreathing bag to eliminate changes in bag volume.

Exercise studies were made with the subject seated on the cycle ergometer, and care was taken to ensure that the height of the pedals and position of the mouthpiece were satisfactory. The subject then breathed room air through the mouthpiece until a steady state was achieved usually within 3 min and in all cases within 4 min. A steady state was judged to be present when the Pco₂ in the end-tidal sample varied to less than ±1 mmHg and the CO₂ excretion in the mixed expired gas varied by less than 20 ml/min. Exercise was then started by pedalling for 2 min at 60 rev./min at 25 kpm/min, the lowest work level setting of the ergometer. When a steady state was achieved, the load was increased by 100 kpm/min at 1 min intervals during continuous exercise. Subjects were asked to continue exercising for as long as possible.

The ventilatory response to CO₂ was measured whilst subjects were seated comfortably on a chair. After a 2 min period of breathing room air through the two-way valve, each subject then rebreathed for 4 min from the 6 litre bag.

Changes in ventilation during exercise were measured on a separate day from the CO₂ response, but both studies were completed within the same week. The protocol was identical for all studies. Although the day-to-day reproducibility of Read's (1967) rebreathing method is well established, there are no similar data for the type of exercise response we used. Therefore, to test the reproducibility, and to guard against unsuspected effects of day-to-day variations, the exercise procedure was repeated several days later in three subjects; one from each end of the range, and one with an intermediate ventilatory response to exercise. Each of these subjects completed the exercise study several times at hourly intervals.

Calculation of minute ventilation during rebreathing was made for each half minute of the
Fig. 1. Change in ventilation per litre of CO₂ production during exercise, plotted against the ventilatory response to CO₂ at rest, for each subject.

Fig. 2. Change in ventilation per litre of O₂ uptake during exercise, plotted against ventilatory response to CO₂ at rest, for each subject.
test, and was plotted against the corresponding $P_{CO_2}$ in expired gas. All gas volumes were corrected to BTPS. The slopes of the CO$_2$ response lines during rebreathing ($S_{CO_2}$) and of the linear portions of the ventilatory changes during exercise ($\Delta V_{E}/\Delta V_{CO_2}$ and $V_{E}/\Delta V_{O_2}$), were calculated by least-squares regression.

**RESULTS**

The range of ventilatory response to CO$_2$ ($S_{CO_2}$) was from 0·81 to 3·11 litres min$^{-1}$ mmHg$^{-1}$. These values all fell within the reported range of response for normal subjects, and the group mean value (mean 1·87; SD 0·61) was comparable with previously reported studies (Table 2).

For the linear portion of the ventilatory response to exercise, when exercise was expressed as CO$_2$ production, the range of response was 16·6–32·0 litres min$^{-1}$ (litres CO$_2$ min$^{-1}$)$^{-1}$ (mean 22·7; SD 5·35). When exercise was expressed as O$_2$ uptake, the range of ventilatory response was 17·0–43·9 litres min$^{-1}$ (litres O$_2$ min$^{-1}$)$^{-1}$ min (mean 29·02; SD 9·07). These values are comparable with those reported by Cunningham (1963), who found a mean value of 23·5 litres min$^{-1}$ (litres O$_2$ min$^{-1}$)$^{-1}$ from the wide range reported in the literature.

**TABLE 2.** Comparison of mean values for $\Delta V_{E}/\Delta P_{CO_2}$ ($S_{CO_2}$) (± SD) by the rebreathing method

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Sample size</th>
<th>$S_{CO_2}$ (litres min$^{-1}$ mm Hg$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Read (1967)</td>
<td>21</td>
<td>2·65 ± 1·21</td>
</tr>
<tr>
<td>Clark (1968)</td>
<td>19</td>
<td>3·29 ± 1·42</td>
</tr>
<tr>
<td>Godfrey, Edwards, Copland &amp; Gross (1971)</td>
<td>7</td>
<td>2·05 ± 0·97</td>
</tr>
<tr>
<td>Saunders, Heilpern &amp; Rebuck (1972)</td>
<td>50</td>
<td>2·17 ± 0·79</td>
</tr>
<tr>
<td>Present study</td>
<td>11</td>
<td>1·87 ± 0·62</td>
</tr>
</tbody>
</table>

The relation between ventilatory response to exercise (expressed as $V_{CO_2}$) and $S_{CO_2}$ is shown in Fig. 1. The slopes of $\Delta V_{E}/\Delta V_{CO_2}$ and $S_{CO_2}$ for each subject showed a highly significant correlation ($r = 0·85; t = 4·74; P<0·001$). When exercise was expressed as O$_2$ uptake (Fig. 2), a similar level of significance was found between the ventilatory response to oxygen uptake and $S_{CO_2}$ ($r = 0·80; t = 4·05; P<0·001$).

The repeatability of ventilatory response to exercise during replicate studies on the same day in three subjects shows close agreement with those found in the initial study. In subject R.C., from the upper extreme of the range, the mean over five tests of ventilatory response was 29·12 litres min$^{-1}$ (litres O$_2$ min$^{-1}$)$^{-1}$ (SD ± 0·93). The two other subjects gave similar reproducible results (A.S.: mean = 22·9; SD ± 0·63 for four tests. M.M.: mean = 17·41; SD ± 0·95 for four tests), despite the wide variation in exercise response between individuals.

**DISCUSSION**

Amongst the individuals we have studied there was a wide range of response to both CO$_2$ and exercise. There was a highly significant correlation between the changes in ventilation during exercise and ventilatory response to CO$_2$ in these subjects, such that the ventilatory response to exercise is greater in those with higher CO$_2$ ($S_{CO_2}$) responsiveness.
The rebreathing method for studying CO₂ response is linear and highly reproducible (Read, 1967; Clark, 1968). Ventilation also rises linearly as the work load is progressively increased (Gray, 1950), deviation from the straight line relationship only arising when work becomes excessive, and arterial lactate concentrations rise above resting values (Asmussen & Neilsen, 1946; Jones, Lal & Naimark, 1963). We found the linear portion of the ventilatory response to increasing exercise to be reproducible on repeated testing, similar results being observed on separate occasions several days apart. Although there was a wide variation in body size and maximum exercise capacity in our subjects, we could find no relationship between these factors and the residual variance in the ventilatory patterns reported.

Examination of other published studies largely support our findings. The effect of CO₂ breathing and moderate exercise has been compared by Matell (1963), who used a steady state response method on his six normal subjects. He concluded that the whole of the slow component of the exercise ventilation could be accounted for by changes in arterial pH, assuming the same sensitivity to such pH changes as he found in CO₂ inhalation. Davies, Gazetopoulos & Oliver (1965) suggested that the contribution of the chemical stimulus to breathing played a diminishing role as exercise proceeds. Their experiments involved prolonged exercise procedures, lasting 50 min, during which time they took no account of temperature changes, which are known to influence the CO₂ response (Cunningham & O'Riordan, 1957).

This modest study is no place to review in depth the chemical and other factors thought to mediate the ventilatory response to exercise, but it is likely that the traditional chemical stimuli to respiration observed in resting subjects also play a major role in the ventilation of rhythmic dynamic exercise. Dejours (1964) has shown that Pa₄CO₂ rises by 2–3 mmHg in mild to moderate exercise, during which the pH falls by an amount greater than can be accounted for by the increase in Pa₄CO₂. Cunningham (1963) has taken mean values for Pa₄CO₂ and pH changes from several studies, and calculated the expected changes in ventilation if the blood was theoretically transfused into resting man. He found that the calculated response was only 60% of that actually found during the exercise procedures in which these PCO₂ and pH changes were observed. However, he noted a wide variation between individuals both in ventilatory response to exercise from which he obtained the mean value, and in the ventilatory response to CO₂ when at rest.

The simplest explanation of our findings would be that those subjects with the greatest ventilation on exercise are those with the greatest chemosensitivity to CO₂ (central or peripheral), but we cannot exclude the possibility that these subjects would also breathe more in response to other stimuli.

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REFERENCES


Ventilation in exercise


