Ventilatory responses to exercise and to carbon dioxide in mitral stenosis before and after valvulotomy: causes of tachypnoea

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Summary

1. The ventilation and cardiac frequency during progressive exercise and the respiratory responses to breathing carbon dioxide have been measured in 33 female patients with mitral stenosis and in 31 control subjects. Compared with the control subjects, the patients' exercise ventilation and cardiac frequency were increased; the exercise tidal volume at standard minute volume, the vital capacity and the ventilatory response to carbon dioxide were reduced. The extent to which the standardized tidal volume was lower during exercise than during breathing carbon dioxide was correlated with the severity of the stenosis, as gauged by the increase in exercise cardiac frequency above the level predicted from anthropometric measurements.

2. Twenty patients were studied postoperatively. In the 12 who showed clinical improvement the exercise ventilation and cardiac frequency were reduced and the exercise tidal volume at a given minute ventilation was increased. The latter change occurred despite a reduction in vital capacity, which was probably a residual effect of thoracotomy. There was no significant change in the response to breathing carbon dioxide. No material change in function was observed in the patients whose condition was not improved by the operation.

3. It is suggested that in mitral stenosis the tachypnoea which occurs during exercise, whilst mainly a mechanical consequence of the reduced vital capacity, is also partly due to pulmonary congestion stimulating intrapulmonary receptors.

Key words: carbon dioxide, exercise, mitral stenosis, tachypnoea, valvulotomy, ventilation.
Abbreviations: $B$, intercept of carbon dioxide response; $FEV_{1.0}$, forced expiratory volume in $1 \mathrm{s}$; $FVC$, forced vital capacity; $S$, respiratory sensitivity to carbon dioxide.

Introduction

The increased ventilatory response to exercise of patients with mitral stenosis has been attributed to a number of causes including enhanced chemical or chemoreceptor drive (Donald, Gloster, Harris, Reeves & Harris, 1961; Cotes, 1955); tachypnoea secondary to a decrease in lung compliance (Palmer, Gee, Mills & Bates, 1963), when it has the effect of minimizing the respiratory work (Marshall, McIlroy & Christie, 1954), and pulmonary congestion leading to stimulation of unidentified pulmonary receptors (Cotes, 1964) which may be in the vicinity of the alveolar capillaries (J receptors; Paintal, 1970). The present study was designed to investigate indirectly the contribution of intrapulmonary receptors in man by comparing the ventilatory response to exercise with that to
rebreathing carbon dioxide; both responses are affected by the altered mechanical properties of the lungs but any pulmonary congestion is probably more marked during exercise than during breathing carbon dioxide. Pulmonary congestion is materially diminished by successful valvulotomy. Thus differences in the pattern of breathing between exercise and rebreathing carbon dioxide, and also between measurements before and after successful valvulotomy, should throw light on the role of congestion in these circumstances. We have also reassessed the response of ventilation and cardiac frequency to exercise in these patients by using indices which are more readily interpretable than some used previously, including the ventilation equivalent (cf. Lloyd & Patrick, 1963) and the ventilation per unit of body surface area or body weight (cf. Cotes, 1972). To this end the responses of the patients have been compared with those of healthy subjects.

Subjects and methods

Outline of the study

The 33 female patients were confirmed cases of pure or predominant mitral stenosis; their ventilatory capacity and responses to exercise were measured a few days before valvulotomy. During the operation pulmonary haemodynamic measurements were also made. In 20 of the patients the measurements on exercise, but not the haemodynamic ones, were repeated 11–15 weeks postoperatively. In addition an independent assessment was made of whether or not the operation had achieved a useful clinical improvement in terms of amelioration of symptoms, increase in daily activity and correction of the valvular abnormality. The 31 healthy control women were drawn from a previous study (Cotes, Hall, Johnson, Jones & Knibbs, 1974). They were of a similar age, height and weight to the patients (Table 1) and did not have physically demanding occupations. All subjects were fully informed about the procedures and their consent was gained before they were admitted to the study; this was carried out with the approval of the local ethical committee.

Anthropometry and ventilatory capacity

Height, weight and, in addition in 15 patients and all the control subjects, skinfold thicknesses at the biceps, triceps, subscapular and supra-iliac sites on the left side of the body, were measured by standard methods (Weiner & Lourie, 1969). In these subjects the sum of the four skinfold thicknesses was used to assess the percentage of body weight as fat and hence the fat-free mass by the empirical method of Durnin & Rahaman (1967);

<table>
<thead>
<tr>
<th>TABLE 1. Mean values and standard deviations for age, anthropometric findings and indices of respiratory and cardiac function in patients and control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mitrail stenosis</strong></td>
</tr>
<tr>
<td><strong>n = 33</strong></td>
</tr>
<tr>
<td><strong>Mean</strong></td>
</tr>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td><strong>Height</strong></td>
</tr>
<tr>
<td><strong>Weight</strong></td>
</tr>
<tr>
<td><strong>Fat-free mass</strong></td>
</tr>
<tr>
<td><strong>Forced expiratory volume</strong></td>
</tr>
<tr>
<td><strong>Forced vital capacity</strong></td>
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<tr>
<td><strong>100 FEV/FVC</strong></td>
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<tr>
<td><strong>Exercise tidal volume</strong></td>
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<tr>
<td><strong>Tidal volume breathing CO2</strong></td>
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<tr>
<td><strong>Exercise ventilation</strong></td>
</tr>
<tr>
<td><strong>Exercise cardiac frequency</strong></td>
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<tr>
<td><strong>Respiratory sensitivity to CO2</strong></td>
</tr>
<tr>
<td><strong>Intercept of CO2 response</strong></td>
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</tbody>
</table>

* Data for fat-free mass relate to 15 subjects, for exercise to 24 subjects and for rebreathing CO2 to 28 subjects.
† At ventilation of 30 l/min.
‡ At O2 uptake of 33 mmol/min.
§ To convert into traditional units (1 min⁻¹ torr⁻¹) divide by 7.5.
|| V130Ex is less than that V130CO2 (P < 0.01).
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this was extended to older age groups, from the
data of Jones et al. (Cotes, 1975).

The forced expiratory volume in 1 s (FEV\textsubscript{1.0})
and the forced vital capacity (FVC) were measured
with a McDermott dry spirometer and corrected to
BTPS (Cotes, 1975).

Haemodynamic measurements

Measurements, which were made under general
anaesthesia as part of the operative procedure,
included mean left atrial pressure, mean pulmonary
arterial pressure, cardiac output (\(Q\)), pulmonary
vascular resistance, the pulmonary wedge pressure,
the valve area and the pressure gradient across the
mitral valve. The subject was supine and the point
of zero pressure was taken as the sternal angle.

Exercise

The patients undertook a progressive exercise
test on a cycle ergometer (Lanooy); the pedalling
rate was 50/min and the load was increased by 10
W/min for a maximum of 10 min. The control
subjects performed similar exercise on a Monark
ergometer. Inspiration was from room air via a gas
meter (Parkinson and Cowan, CD4), low-dead-
space and low-resistance valve box and face mask
(Baxter Pneuseal). The suction during inspiration,
at a flow rate of 85 litres/min, was less than 0.1
kPa. Expiration was to atmosphere via a gas-
mixing chamber (capacity 4 litres) from which
mixed expired gas was drawn continuously through
an infrared CO\textsubscript{2} analyser (Hartmann and Braun,
Uras 4) and a paramagnetic O\textsubscript{2} analyser (Ser-
vomex OA250). The electrocardiogram was recor-
ded from bipolar chest leads. The exercise was
terminated when the subject expressed discomfort
or fatigue, became dyspnocic or pale, or a workload
of 100 W was attained. The results were analysed
in terms of the linear parts of the relationships
between expired minute ventilation, or cardiac
frequency with oxygen uptake, and of minute
ventilation with tidal volume (Hey plot). The
methods used and reference values for exercise
cardiac frequency were those reported previously
(Cotes \textit{et al.}, 1974).

Response to hypercapnia

The ventilatory response to carbon dioxide was
assessed by rebreathing O\textsubscript{2} + CO\textsubscript{2} (95:5, v/v)
from a 6 litres bag contained in a Perspex box
(Read, 1967). The box was connected to the gas
meter via one-way valves so that ventilation and
respiratory frequency could be measured from the
resulting displacement of air (Donald Christie box).
Carbon dioxide and oxygen were sampled con-
tinuously at the mouthpiece and then returned to
the bottom of the bag. The rebreathing was
terminated when the P\textsubscript{CO\textsubscript{2}} exceeded 8.6 kPa or the
subject experienced discomfort. The P\textsubscript{O\textsubscript{2}} never fell
below 27 kPa. The expired minute ventilation and
tidal volume at BTPS were calculated at each 0.5
min; the P\textsubscript{CO\textsubscript{2}} was corrected for the collision
broadening effect of oxygen (Patrick, 1963). The
carbon dioxide sensitivity was expressed in terms of
the slope (\(S\)) and the intercept (\(B\)) of the linear part
of the graph relating the ventilation (\(V_e\)) to the
P\textsubscript{CO\textsubscript{2}}: \(V_e = S(P_{CO_2} - B)\).

In the interpretation of results the 5% level of
probability was accepted as significant.

Results

Pre-operative values for the patients and control
subjects (Table 1)

The ranges of ages, weights and heights of both
patients and control subjects were wide, but the
distributions were comparable with no significant
difference between the mean values. All the values
for the control subjects agree closely with those
expected for healthy women of this mean age and
body size (Cotes, 1975). The ventilatory capacity
of the patients was significantly reduced
(P < 0.001) with FEV\textsubscript{1.0} and FVC values being about
only two-thirds of those in the control subjects. By
contrast the ratio FEV\textsubscript{1.0}/FVC (FEV\textsubscript{\%}) was the
same in both groups.

The cardiopulmonary response to progressive
exercise is reported in terms of the cardiac
frequency and minute ventilation at the oxygen
uptake of 33 mmol/min (0.75 litre/min). Twenty-
four patients achieved this rate of metabolism or
came sufficiently near to it for extrapolation to be
considered justifiable. Twenty of the patients were
in normal rhythm; four were in atrial fibrillation
controlled by digoxin, which did not significantly
affect either the cardiac frequency or the minute
ventilation. For both indices the values were
significantly higher than those for the control
subjects (P < 0.001; Table 1).

The mean values of \(S\) and \(B\) were both
significantly reduced in the patients with mitral
stenosis ($P < 0.001$). $S$ was related to the vital capacity in the control subjects ($P < 0.05$), but in the patients this relationship was not significant.

The pattern of breathing during exercise and in response to carbon dioxide was analysed in terms of the tidal volume at a ventilation of 30 litres/min ($V_{130}$, Cotes, 1972). The tidal volume was less during exercise than during carbon dioxide rebreathing in both groups, the tidal volumes being smaller in the patients (Table 1). In the control subjects the indices of tidal volume were significantly correlated with vital capacity, and the same relationships also described the data for the patients, which were not by themselves significant. The combined relationships are given in Fig. 1.

**Haemodynamic findings (Table 2)**

The mean results for the haemodynamic studies on the patients at operation are given in Table 2. The individual values were related to the difference...
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Table 2. Haemodynamic data for patients subjected to operation

To convert mmHg to kPa divide by 7.5.

<table>
<thead>
<tr>
<th>Index</th>
<th>Number</th>
<th>Mean and range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary arterial mean pressure (mmHg)</td>
<td>19</td>
<td>23.9 (8-36)</td>
</tr>
<tr>
<td>Left atrial mean pressure (mmHg)</td>
<td>18</td>
<td>13.3 (4-20)</td>
</tr>
<tr>
<td>Gradient across valve (mmHg)</td>
<td>19</td>
<td>9.6 (4-18)</td>
</tr>
<tr>
<td>Valve area (cm²)</td>
<td>17</td>
<td>1.29 (2.4-0.7)</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>13</td>
<td>40.5 (47.1-33.1)</td>
</tr>
<tr>
<td>Exercise cardiac frequency* (min⁻¹)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observed</td>
<td>13</td>
<td>132.9 (172)</td>
</tr>
<tr>
<td>Predicted</td>
<td>13</td>
<td>105.3</td>
</tr>
</tbody>
</table>

* At O₂ uptake of 22 mmol/min (0.5 l/min)

in $V_{130}$ between exercise and carbon dioxide rebreathing ($V_{130, CO₂} - V_{130, ex.}$), which appeared to reflect the haemodynamic disturbance; however, for none of the haemodynamic measurements either separately or in combination did those relationships reach the 5% level of significance. By contrast, for the 13 patients on whom complete data were available the tidal volume difference was positively correlated with the extent to which the exercise cardiac frequency exceeded the expected value ($P < 0.05$, Fig. 2). This was not the case for the control subjects.

Comparison of pre- and post-operative findings

On clinical grounds the valvulotomy was considered to have been successful in 12 of the 20 patients who were studied postoperatively, and in the remainder there was either no clinical improvement or the valve appeared to have become incompetent. In the group showing clinical improvement both the exercise ventilation and the exercise cardiac frequency were significantly reduced; the exercise tidal volume was increased (Table 3). The response to rebreathing carbon dioxide, including the respiratory sensitivity ($S$) and the pattern of breathing were unaltered, whereas the ventilatory capacity was further impaired. In the group not showing clinical improvement there was suggestive evidence of deterioration in some of the indices of pulmonary function but only in the case of the threshold response to carbon dioxide ($B$) did the change reach the 5% level of probability (Table 3). Thirteen of the patients who underwent valvulotomy were re-tested 44–50 weeks after the operation, nine from the successful group and four from the unsuccessful group. Compared with the earlier postoperative results the exercise ventilation was somewhat reduced in both groups, but overall there was no significant change in the patients’ responses between the two postoperative studies.

Discussion

The respiratory function of the present patients with mitral stenosis is typical of this condition, including the reduction in ventilatory capacity, the increase both in exercise ventilation and cardiac frequency and the reduced respiratory response to rebreathing carbon dioxide (MacIntosh, Sinnott, Milne & Reid, 1958; Stock & Kennedy, 1959; Bishop & Wade, 1963; Pauli, Noe & Coates, 1960). The present results extend these observations by relating the exercise ventilation and cardiac frequency to the uptake of oxygen to provide indices in a standard form which can be
compared with the results for other subjects and conditions. Thus during exercise at a rate of energy expenditure which requires an uptake of oxygen of 33 mmol/min (0.75 litre/min) the ventilation of the present patients exceeds that of healthy persons by, on average, 54% and the cardiac frequency by, on average, 31%, when both are expressed in the form 100 ΔV/ΔR (Oldham, 1968). The corresponding changes for patients with severe airways obstruction due to chronic bronchitis have been reported as 21% and 14% respectively (Spiro, Hahn, Edwards & Pride, 1975). Thus in both conditions the proportional increase in the ventilation exceeds that in the cardiac frequency, but the deviations from normal are greater for the primary cardiac than for the primary respiratory disorder.

The respiratory sensitivity to carbon dioxide (S) and the pattern of breathing described by the $V_{130}$ both reflect in part the mechanical properties of the lung. On this account in healthy subjects the indices are positively correlated with the vital capacity (Patrick & Cotes, 1976; Cotes, Johnson & MacDonald, 1970). Mitral stenosis, by causing pulmonary congestion and interstitial oedema, reduces the vital capacity and part of the reduced respiratory sensitivity and tidal volume are probably due to this change. The low values for $V_{130}$ observed pre-operatively are those to be expected for the associated reduction in vital capacity and the difference from normal disappears when correction is made for differences in vital capacity. The reduced respiratory sensitivity to carbon dioxide is not fully explicable by such correction, and this is also the case for the change in tidal volume after valvulotomy. Thus the alteration in lung distensibility cannot account for all the reduction in tidal volume or carbon dioxide sensitivity, and other consequences of pulmonary congestion may be responsible. The congestion is a feature of mitral stenosis compared with healthy subjects; it is probably greater during exercise than during rebreathing carbon dioxide, and is likely to be ameliorated by successful valvulotomy. Thus a difference in $V_{130}$ between exercise and rebreathing carbon dioxide, which was related to the severity of the stenosis, would suggest that the pulmonary congestion contributed to the tachypnoea of mitral stenosis, as would a post-valvulotomy reduction in exercise $V_{130}$ which was greater than that to be expected from any associated change in vital capacity.

In the event in patients in whom the operation was clinically successful the exercise $V_{130}$ was reduced, although there was no change in vital capacity, but the $V_{130}$ was unaltered in patients in whom the operation was not successful. In addition

<p>| TABLE 3. Mitral stenosis: effects of valvulotomy on cardiopulmonary response to exercise and rebreathing carbon dioxide |
|-------------------------------------------------|-------------------------------------------------|---------------------------------|
| N.S. = not significant.                        | Pre-operative                                  | Postoperative                  |</p>
<table>
<thead>
<tr>
<th>Mean</th>
<th>sd</th>
<th>Mean</th>
<th>sd</th>
<th>Significance (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise ventilation ($V_{130}$, l/min)</td>
<td>22.1 ± 4.2</td>
<td>17.3 ± 2.9</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Exercise cardiac frequency ($f_{130}$, min⁻¹)</td>
<td>125 ± 26</td>
<td>101 ± 15</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Exercise tidal volume ($V_{130}$, l/min)</td>
<td>1.05 ± 0.12</td>
<td>1.14 ± 0.12</td>
<td>&lt;0.02</td>
<td></td>
</tr>
<tr>
<td>Tidal volume breathing CO₂ ($V_{130}$, l/min)</td>
<td>1.51 ± 0.31</td>
<td>1.47 ± 0.27</td>
<td>N.S.</td>
<td></td>
</tr>
<tr>
<td>Respiratory sensitivity to CO₂ ($S$, l/KPa)</td>
<td>10.0 ± 4.3</td>
<td>10.6 ± 3.05</td>
<td>N.S.</td>
<td></td>
</tr>
<tr>
<td>Intercept of CO₂ response ($B$, KPa)</td>
<td>4.3 ± 0.75</td>
<td>4.5 ± 1.08</td>
<td>N.S.</td>
<td></td>
</tr>
<tr>
<td>Forced expiratory volume ($FEV_{130}$, l)</td>
<td>2.07 ± 0.70</td>
<td>1.84 ± 0.64</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Forced vital capacity ($FVC_{130}$, l)</td>
<td>2.68 ± 0.69</td>
<td>2.38 ± 0.67</td>
<td>&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>

* At O₂ uptake of 22 mmol/min (0.5 l/min).
† At ventilation of 30 l/min.
the difference in $V_{T0}$ between exercise and rebreathing carbon dioxide was significantly correlated with the extent to which the exercise cardiac frequency exceeded its predicted value, and hence with the severity of the stenosis (cf. Bishop & Wade, 1963).

An association between indices of pulmonary congestion and exercise tachypnoea which obtains both between subjects studied on a cross-sectional basis and within subjects studied before and after successful valvulotomy is evidence that the two are causally related. Reed (1975) has shown that a similar conclusion may be drawn from the data of Gazetopulos, Salonikides & Davies (1974). The mechanism might relate to ventilation–perfusion inequality contributing to hypoxaemia, but there is evidence that the latter does not affect the relationship of ventilation minute volume to tidal volume (Hey, Lloyd, Cunningham, Jukes & Bolton, 1966; Petersen & Cunningham, 1976). Alternatively the additional pulmonary congestion due to the exercise might stimulate receptors within the thorax or chest wall so as to alter the pattern of breathing to reduce the tidal volume and increase the respiratory frequency. A response of this type might be due to an increase in the elastic work of breathing, but other evidence suggests that this is unlikely (Cotes et al., 1970). The vascular disturbance is almost certainly registered by intravascular receptors, which in the case of stimulation of the juxtacapillary (J) receptors gives rise to tachypnoea in experimental animals (Paintal, 1970). There is no certainty that this response also occurs in man. Tachypnoea is a feature of several conditions where there is abnormality of the lung parenchyma including, in addition to mitral stenosis, beryllium disease (Cotes et al., 1970) and left ventricular failure. A response to intrapulmonary receptor stimulation seems to us to be the most probable mechanism.

This conclusion is of theoretical importance in suggesting that the abnormal ventilatory response to exercise of patients with mitral stenosis and probably other conditions is due in part to receptors in the lung. Their properties are therefore of immediate concern to clinical physiologists who up to now have mainly been interested in the mechanical and gas-exchanging characteristics of this part of the lung. The results are also of practical importance in contributing to understanding of the pattern of breathing in patients with tachypnoea, and hence to the differential diagnosis and treatment of the several conditions which may be responsible.

**Acknowledgments**

We are indebted to Dr L. G. Davies for introductions to the patients and for details of the haemodynamic findings, to Dr H. M. Foreman and Dr A. Seaton for the use of facilities at Sully Hospital and to Mr G. Berry for statistical advice. The work undertaken by J.W.R. was a part requirement for the Ph.D. of the Welsh National School of Medicine.

**References**


