Anatomical dead space, ventilatory pattern, and exercise capacity in chronic heart failure

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Abstract

Background—Patients with chronic heart failure have an excessive ventilatory response to exercise, characterised by an increase in the slope of the relation between ventilation and carbon dioxide production (VE/VCO₂ slope). Patients have an altered respiratory pattern with an increased respiratory rate (f) at a given tidal volume (VT), which may result in increased anatomical dead space ventilation.

Methods—The ventilatory responses in 88 patients with chronic heart failure and 43 age matched controls during maximal incremental treadmill exercise were analysed. Peak oxygen consumption (VO₂), VE/VCO₂ slope, and the slope of the relation between f and VT were derived. Anatomical dead space was estimated from a standard formula and anatomical dead space ventilation calculated.

Results—Peak VO₂ was greater (mean (SD)) (33·2 (8·5) v 19·4 (6·7) ml/min/kg; P < 0·001) and the VE/VCO₂ slope lower in the controls (25·96 (4·16) v 35·14 (9·80); P < 0·001). During matched submaximal exercise VT was higher (1·97 (0·92) v 1·68 (0·62) l; P < 0·05) and f lower in the controls (18·23 (6·48) v 24·28 (7·58); P < 0·001). At peak exercise there was no difference in f, but VT was higher in the controls (2·66 (0·97) v 1·99 (0·61) l; P < 0·001). The VT/f slope was the same (0·04 (0·04)) in both groups. The intercept of the relation was greater for the control group (1·31 (1·28) v 0·59 (0·83); P < 0·001). Anatomical dead space ventilation was lower in the controls at submaximal work load (4·17 (1·56) v 5·58 (1·93) l/min; P < 0·001). At peak exercise anatomical dead space ventilation was the same in both groups, but was lower expressed as a percentage of total VE in the control group (9·8 (3·3) v 13·5 (4·0); P < 0·001). There were weak relations within the heart failure group alone between VT/f slope and peak VO₂ and VE/VCO₂ slope.

Conclusions—The relation between anatomical dead space ventilation and VE/VCO₂ slope is expected: as f increases, so do VE/VCO₂ slope and anatomical dead space ventilation. The VT/f slope was the same in patients with chronic heart failure and controls, so change in respiratory pattern cannot explain the increase in VE/VCO₂ slope. The stimulus causing the increased f has yet to be identified.

Keywords: chronic heart failure; dead space; ventilatory pattern; exercise capacity

The excessive ventilatory response to exercise in chronic heart failure is well characterised by an increase in the slope relating minute ventilation (VE) to carbon dioxide production (VCO₂). This slope is described by a linear regression function with an r value in excess of 0·9 in almost all cases. The increase in the VE/VCO₂ slope is closely related to the degree of exercise limitation as characterised by a reduction in peak oxygen consumption (peak VO₂).1,2 The cause of the increased ventilation is not definitively established, although an increase in dead space ventilation has been proposed.1,3

One possible contribution to an increase in dead space ventilation is that of anatomical dead space (ADS).4 Patients with heart failure have an abnormal breathing pattern: at any given VE, tidal volume (VT) is smaller and respiratory frequency (f) is increased.5 As a result, ADS, even if considered fixed in absolute terms, is ventilated more often, and as a proportion of total ventilation, anatomical dead space ventilation is increased.

We wanted to explore the possible contribution of the altered ventilatory pattern to the increased VE/VCO₂ slope, using the slope of the relation between respiratory rate and tidal volume6 to describe the ventilatory pattern.

Patients and methods

We examined the responses to exercise of 88 patients with chronic heart failure of mean (SD) age 58·6 (11·6) years and compared them with 43 matched controls of mean (SD) age 54·6 (10·5) years. The table gives patient details. Patients were referred for exercise testing as part of their routine assessment. The controls were volunteers from among hospital staff, and in addition some were recruited from among men attending for routine medicals arranged by their companies. These controls gave fully informed signed consent before exercise testing.

Heart failure was diagnosed on the basis of decreased exercise capacity in the presence of impaired left ventricular dysfunction as shown by echocardiograms, radionuclide ventriculography scans, or cardiac catheterisation. All patients were stable for a minimum of 6 weeks before exercise testing. None was oedematous.
nor limited by symptoms of angina or claudication. Patients with intercurrent illness or documented lung pathology were excluded.

Participants undertook incremental treadmill exercise tests using a Bruce protocol modified by the addition of a "stage 0" at onset—that is 3 min exercise at 1·61 km/h with a 5% gradient. Exercise to exhaustion was encouraged. Participants breathed through a one way valve connected to a respiratory mass spectrometer (Amis 2000; Odense, Denmark). Metabolic gas exchange (VO\(_2\), VCO\(_2\)) and VE were measured on line every 10 s using the inert gas dilution method.\(^9\) In addition, the mass spectrometer allowed continuous monitoring of fractional carbon dioxide concentration at the mouth. Breathing rate was measured from the capnograph, and VT was calculated from VE and f.

ADS was estimated from the standard formula, ADS = weight × 2·2 + age.\(^{11}\) ADS ventilation (VADS) was calculated from ADS × f, and was also expressed as a percentage of VE (VADS/VE × 100%). The values recorded were averages of the last 30 s of each stage of exercise and at peak exercise.

The VE/VCO\(_2\) slope and peak VO\(_2\) were calculated for each test. The slope of the relation between VT and f was also derived. After exercise the patient was asked for the dominant symptom at peak exercise. The first response was recorded. Quoted results for matched submaximal exercise were taken from the end of stage 1 of exercise.

Results are expressed as means (SD). Between groups comparisons were made with unpaired Student's t test; within group comparisons were made with paired t tests. Correlations were calculated by the least squares method. The null hypothesis was rejected where P < 0·05.

### Results

The table gives the exercise results. The

<table>
<thead>
<tr>
<th>Characteristics of patients and controls</th>
<th>Patients (n = 88)</th>
<th>Controls (n = 43)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age (years)</td>
<td>58·6 (11·6)</td>
<td>54·6 (10·5)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (SD) weight (kg)</td>
<td>78·6 (14·2)</td>
<td>79·5 (13·7)</td>
<td>NS</td>
</tr>
<tr>
<td>Diagnosis</td>
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<tr>
<td>Dilated cardiomyopathy</td>
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<tr>
<td>Ischaemic heart disease</td>
<td>47</td>
<td></td>
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<tr>
<td>Mean (SD) left ventricular ejection fraction (%)</td>
<td>28·2 (14·2)</td>
<td>25·9 (10·5)</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td>Mean (SD) cardiothoracic ratio</td>
<td>0·57 (0·07)</td>
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<tr>
<td>Drugs*</td>
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<tr>
<td>Frusenide</td>
<td>81·8 (72·7)</td>
<td></td>
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<tr>
<td>Angiotensin converting enzyme inhibitor</td>
<td>65</td>
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<tr>
<td>Warfarin</td>
<td>23</td>
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<td>Amiodarone</td>
<td>16</td>
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<td>New York Heart Association</td>
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<td>I</td>
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<td>II</td>
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<td>III</td>
<td>35</td>
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<td>IV</td>
<td>14</td>
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</tr>
<tr>
<td>Mean (SD) peak VO(_2) (ml/min/kg)</td>
<td>19·1 (6·7)</td>
<td>33·2 (8·5)</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td>Mean (SD) exercise time (s)</td>
<td>499 (210)</td>
<td>837 (385)</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td>Mean (SD) VE/VCO(_2) slope</td>
<td>35·14 (9·80)</td>
<td>25·96 (4·16)</td>
<td>&lt;0·001</td>
</tr>
</tbody>
</table>

*The mean (SD) daily dose of frusenide is given; other values refer to the number of patients taking each drug. Peak VO\(_2\), maximum rate of oxygen consumption; VE/VCO\(_2\), slope, of the relation between ventilation and carbon dioxide production; NS, not significant.

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Figure 1  (A) Respiratory frequency (f) and (B) tidal volume (VT) at rest, during matched submaximal exercise, and peak exercise in patients with chronic heart failure and controls. Bars are standard deviations.

Regression coefficient for the VE/VCO\(_2\) relation was greater than 0·94 in all cases. As previously reported,\(^{13}\) there was a negative relation between peak VO\(_2\) and VE/VCO\(_2\) slope (r = 0·59; P < 0·001) in patients with heart failure.

Figure 1 shows the VT and f at rest, matched submaximal exercise, and peak exercise in patients with heart failure and controls. At matched work loads during exercise VT was greater and the f slower in the controls.

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Figure 2  Anatomical dead space ventilation (VADS) in (A) l/min and as a proportion of total minute ventilation (V\(_{E}\)) (B) in patients with chronic heart failure and controls.
Anatomical dead space, ventilatory pattern, and exercise capacity in chronic heart failure

At peak exercise both groups had similar respiratory rates, but the control group has a much higher VT and hence VE.

ADS was estimated as 231.6 (33.4) in patients with heart failure and 229.4 (28.3) in the controls (P = NS). Figure 2 shows VADS values. As f is greater in heart failure at submaximal exercise, so is VADS, although as a percentage of VE, VADS is not significantly different from controls, reflecting the greater total VE as submaximal work loads in chronic heart failure. As peak f is similar in patients and controls, peak VADS is also the same in both groups; as total VE is greater in the controls, then VADS as a percentage of total ventilation is higher in patients with heart failure. The VT/f relation was much less strong than that between VE and VCO2. The mean (SD) correlation coefficient was 0.55 (0.26) for patients with heart failure and 0.44 (0.33) for the controls. The mean slope was the same (0.04 (0.04)) in both groups. The intercept on the y axis (that is, VT when f is zero) was 0.59 (0.83) in the patients with chronic heart failure and 1.31 (1.28) in the controls (P < 0.001).

We could identify a break point in the VT/f relation in only four patients and in two controls, unlike the situation reported by Yokoyama et al10 who reported a point at which f started to increase relative to VT, which corresponded to the onset of dyspnoea. The slope of the VT/f relation was the same in the patients stopped by breathlessness (70-5%) and in those stopped by fatigue (29-5%) (0.03 (0.03) in both groups). Figure 3 shows the data plotted for the two groups, which may give the misleading impression of such a break point; this plot shows that the VT/f relation is similar in patients and controls (0.04 (0.04) in each group), but is displaced downwards and to the right in heart failure.

CORRELATES OF VENTILATORY RESPONSE

There was a weak relation between the VT/f slope and both peak VO2, (r = 0.29; P = 0.006) and VE/VCO2 slope (r = -0.30; P = 0.005). There was no correlation between peak VADS and either peak VO2 or VE/VCO2 slope in patients with heart failure. Expressed as a proportion of VE, there was a significant negative relation with peak VO2 (r = -0.52; P < 0.001). Submaximal VADS correlated with peak VO2 and VE/VCO2 slope (fig 4).

Discussion

The pathophysiological mechanism underlying the increased VE/VCO2 slope in chronic heart failure remains unexplained. In the cardiological literature, reference to the alveolar ventilation equation—that is VE/VCO2 = 863/(PacO2 × (1 - Vd/VT)), where PacO2 is arterial carbon dioxide tension, Vd/VT is dead space as a fraction of VT, and 863 is a constant, is taken as evidence that the cause of the increased VE/VCO2 slope in the face of near normal arterial blood gas tensions12,13 must be increased dead space.14 A major contribution to such an increase in dead space ventilation could arise from an increase in VADS consequent on a change in ventilatory pattern. If this was the case, then it might be anticipated that the relation between VT and f would be shallower in patients with chronic heart failure with an increase in VE being met predominantly by a rise in f rather than VT. It might be thought that the slope of this relation would correlate with exercise capacity and VE/VCO2 slope.

In the present study we have shown no difference between the VT/f slope in patients with chronic heart failure and controls. There were weak relations within the heart failure group alone between VT/f slope and peak VO2 and VE/VCO2 slope. This relation disappeared when all participants were analysed together. The intercept value was higher for the controls, indicating that VT was about 0.72 higher in controls, but there was considerable overlap between the two groups. The VT/f slope was the same regardless of symptoms at peak exercise, which fits with our earlier suggestion that breathlessness and fatigue represent a single physiological process, perhaps not related to ventilatory abnormality.15

We found that both groups stopped exercising when the peak f was about the same.
Patients with chronic heart failure reached this point at a lower VT, and thus with a higher VADS as a proportion of VE. Conversely, at matched work load, as ventilation was greater in the patients with heart failure, the greater minute VADS was a similar percentage of total VE. The relation between dead space during submaximal exercise and exercise capacity is expected; submaximal VADS increases as f increases. As f increases at a given level of VCO₂, so does VE/VCO₂; given the negative relation that exists in heart failure between VE/VCO₂ slope and peak VO₂, it is inevitable that VADS and peak VO₂ will correlate.

These results suggest that VADS is not an important contributor to the increased ventilatory response to exercise in chronic heart failure. Changes in VADS may result from a change in ventilatory pattern, but the VT/f slope was the same in patients with heart failure and controls. We have previously shown that there is no relation between altered respiratory pattern and the VE/VCO₂ slope in normal controls. Rather than the increase in VADS leading to an increased VE/VCO₂ slope, both can be thought of as arising as a consequence of an alteration in ventilatory pattern. The nature of the stimulus causing the increased f has yet to be identified.