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

A L Clark, T P Chua, A J S Coats

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 ($\dot{V}E/\dot{V}CO_2$ 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 ($\dot{V}O_2$), $\dot{V}E/\dot{V}CO_2$ 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 $\dot{V}O_2$ was greater (mean (SD)) (33·2 (8·5) v 19·4 (6·7) ml/min/kg; P < 0·001) and the $\dot{V}E/\dot{V}CO_2$ 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 1·90 (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 $\dot{V}E$ 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 $\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ slope.

Conclusions—The relation between anatomical dead space ventilation and $\dot{V}E/\dot{V}CO_2$ slope is expected: as f increases, so do $\dot{V}E/\dot{V}CO_2$ 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 $\dot{V}E/\dot{V}CO_2$ slope. The stimulus causing the increased f has yet to be identified.

The excessive ventilatory response to exercise in chronic heart failure is well characterised by an increase in the slope relating minute ventilation ($\dot{V}E$) to carbon dioxide production ($\dot{V}CO_2$). 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 $\dot{V}E/\dot{V}CO_2$ slope is closely related to the degree of exercise limitation as characterised by a reduction in peak oxygen consumption (peak $\dot{V}O_2$).[1 2] The cause of the increased ventilation is not definitively established, although an increase in dead space ventilation has been proposed.[3-5]

One possible contribution to an increase in dead space ventilation is that of anatomical dead space (ADS).[6] Patients with heart failure have an abnormal breathing pattern: at any given $\dot{V}E$, tidal volume (VT) is smaller and respiratory frequency (f) is increased.[3 7] 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 $\dot{V}E/\dot{V}CO_2$ slope, using the slope of the relation between respiratory rate and tidal volume[8] 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

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Characteristics of patients and controls

	Patients (n = 88)	Controls (n = 43)	p value
Mean (SD) age (years)	58·6 (11·6)	54·6 (10·5)	NS
Mean (SD) weight (kg)	78·6 (14·2)	79·5 (13·7)	NS
Diagnosis			
Dilated cardiomyopathy	41		
Ischaemic heart disease	47		
Mean (SD) left ventricular ejection fraction (%)	28·2 (14·2)		
Mean (SD) cardiothoracic ratio	0·57 (0·07)		
Drugs*			
Frusemide	81·8 (72·7)		
Angiotensin converting enzyme inhibitor	65		
Warfarin	23		
Digoxin	20		
Amiodarone	16		
New York Heart Association			
I	16		
II	23		
III	35		
IV	14		
Mean (SD) peak $\dot{V}O_2$ (ml/min/kg)	19·1(6·7)	33·2(8·5)	<0·001
Mean (SD) exercise time (s)	499 (210)	837 (185)	<0·001
Mean (SD) $\dot{V}E/\dot{V}CO_2$ slope	35·14 (9·80)	25·96 (4·16)	<0·001

*The mean (SD) daily dose of frusemide is given; other values refer to the number of patients taking each drug. Peak $\dot{V}O_2$, maximum rate of oxygen consumption; $\dot{V}E/\dot{V}CO_2$ slope, slope of the relation between ventilation and carbon dioxide production; NS, not significant.

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 ($\dot{V}O_2$, $\dot{V}CO_2$) and $\dot{V}E$ were measured on line every 10 s using the inert gas dilution method.[9] [10] 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 $\dot{V}E$ and f.

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

The $\dot{V}E/\dot{V}CO_2$ slope and peak $\dot{V}O_2$ 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

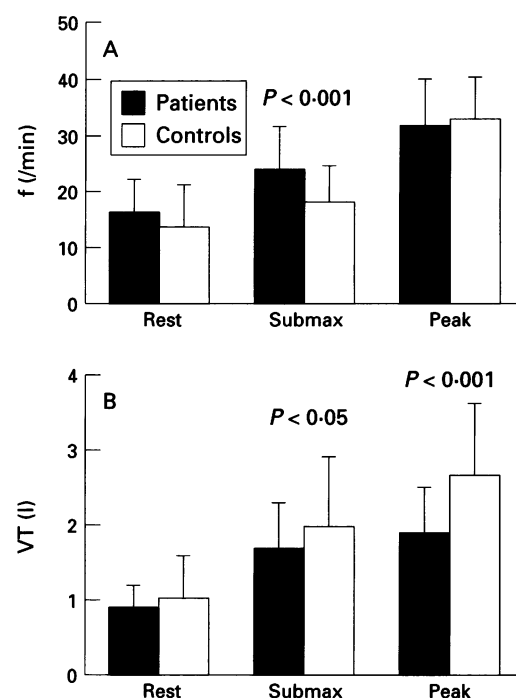The table gives the exercise results. The

Figure 1 (A) Respiratory frequency (f) and (B) tidal volume (V_T) 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 $\dot{V}E/\dot{V}CO_2$ relation was greater than 0·94 in all cases. As previously reported,[1] [2] there was a negative relation between peak $\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ slope ($r = -0·59$; P < 0·001) in patients with heart failure.

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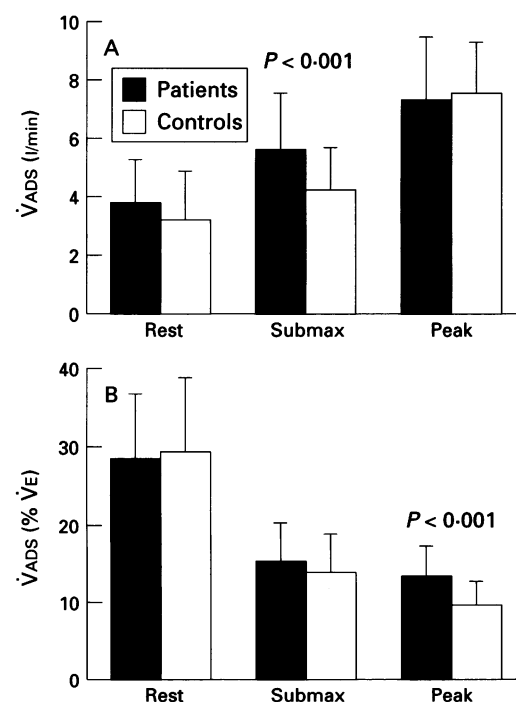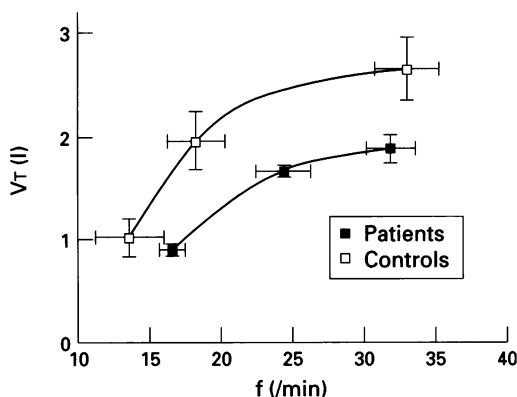

Figure 2 Anatomical dead space ventilation ($\dot{V}ADS$) in (A) l/min and as a proportion of total minute ventilation ($\dot{V}E$) (B) in patients with chronic heart failure and controls.

Figure 3 Relation between tidal volume (VT) and respiratory frequency (f) in patients with chronic heart failure and controls. Values are means (95% confidence intervals (CI)). Bars are 95%.

Yokoyama *et al*,[8] who reported a point at which f started to increase relative to V_T, which corresponded to the onset of dyspnoea. The slope of the V_T/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 subgroups). 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 V_T/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.

At peak exercise both groups had similar respiratory rates, but the control group has a much higher $\dot{V}_T$ and hence $\dot{V}_E$.

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 $\dot{V}_{ADS}$ values. As f is greater in heart failure at submaximal exercise, so is $\dot{V}_{ADS}$, although as a percentage of $\dot{V}_E$, $\dot{V}_{ADS}$ is not significantly different from controls, reflecting the greater total $\dot{V}_E$ as submaximal work loads in chronic heart failure. As peak f is similar in patients and controls, peak $\dot{V}_{ADS}$ is also the same in both groups; as total $\dot{V}_E$ is greater in the controls, then $\dot{V}_{ADS}$ as a percentage of total ventilation is higher in patients with heart failure.

The V_T/f relation was much less strong than that between $\dot{V}_E$ and $\dot{V}_{CO_2}$. 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, V_T when f is zero) was 0·59 (0·83) l 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 $\dot{V}_T$/f relation in only four patients and in two controls, unlike the situation reported by

CORRELATES OF VENTILATORY RESPONSE
There was a weak relation between the V_T/f slope and both peak $\dot{V}_{O_2}$ (r = 0·29; P = 0·006) and $\dot{V}_E$/$\dot{V}_{CO_2}$ slope (r = − 0·30; P = 0·005). There was no correlation between peak $\dot{V}_{ADS}$ and either peak $\dot{V}_{O_2}$ or $\dot{V}_E$/$\dot{V}_{CO_2}$ slope in patients with heart failure. Expressed as a proportion of $\dot{V}_E$, there was a significant negative relation with peak $\dot{V}_{O_2}$ (r = − 0·52; P < 0·001). Submaximal $\dot{V}_{ADS}$ correlated with peak $\dot{V}_{O_2}$ and $\dot{V}_E$/$\dot{V}_{CO_2}$ slope (fig 4).

Discussion
The pathophysiological mechanism underlying the increased $\dot{V}_E$/$\dot{V}_{CO_2}$ slope in chronic heart failure remains unexplained. In the cardiological literature, reference to the alveolar ventilation equation—that is $\dot{V}_E$/$\dot{V}_{CO_2}$ = 863/(Pa_{CO_2} × (1 − V_D/V_T), where Pa_{CO_2} is arterial carbon dioxide tension, V_D/V_T is dead space as a fraction of V_T, and 863 is a constant, is taken as evidence that the cause of the increased $\dot{V}_E$/$\dot{V}_{CO_2}$ slope in the face of near normal arterial blood gas tensions[12 13] must be increased dead space.[3-5] A major contribution to such an increase in dead space ventilation could arise from an increase in $\dot{V}_{ADS}$ consequent on a change in ventilatory pattern. If this was the case, then it might be anticipated that the relation between V_T and f would be shallower in patients with chronic heart failure with an increase in $\dot{V}_E$ being met predominantly by a rise in f rather than $\dot{V}_T$. It might be thought that the slope of this relation would correlate with exercise capacity and $\dot{V}_E$/$\dot{V}_{CO_2}$ slope.

In the present study we have shown no difference between the V_T/f slope in patients with chronic heart failure and controls. There were weak relations within the heart failure group alone between V_T/f slope and peak $\dot{V}_{O_2}$ and $\dot{V}_E$/$\dot{V}_{CO_2}$ slope. This relation disappeared when all participants were analysed together. The intercept value was higher for the controls, indicating that V_T was about 0·72 l greater in controls, but there was considerable overlap between the two groups. The V_T/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.[14]

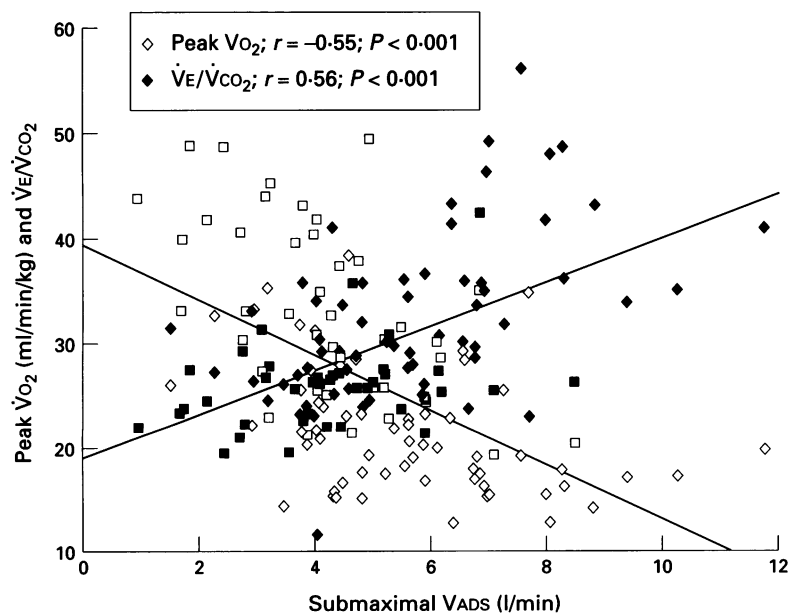We found that both groups stopped exercising when the peak f was about the same.

Figure 4 Submaximal anatomical dead space ventilation ($\dot{V}_{ADS}$) as a "predictor" of peak oxygen consumption (peak $\dot{V}_{O_2}$) and the $\dot{V}_E$/$\dot{V}_{CO_2}$ slope. Open symbols refer to peak $\dot{V}_{O_2}$ and filled symbols to the $\dot{V}_E$/$\dot{V}_{CO_2}$ slope. Diamonds refer to patients and squares to controls.

Patients with chronic heart failure reached this point at a lower V_T, and thus with a higher $\dot{V}_{ADS}$ as a proportion of $\dot{V}_E$. Conversely, at matched work load, as ventilation was greater in the patients with heart failure, the greater minute $\dot{V}_{ADS}$ was a similar *percentage* of total $\dot{V}_E$. The relation between dead space during submaximal exercise and exercise capacity is expected; submaximal $\dot{V}_{ADS}$ increases as f increases. As f increases at a given level of $\dot{V}_{CO_2}$, so does $\dot{V}_E/\dot{V}_{CO_2}$; given the negative relation that exists in heart failure between $\dot{V}_E/\dot{V}_{CO_2}$ slope and peak $\dot{V}_{O_2}$, it is inevitable that $\dot{V}_{ADS}$ and peak $\dot{V}_{O_2}$ will correlate.

These results suggest that $\dot{V}_{ADS}$ is not an important contributor to the increased ventilatory response to exercise in chronic heart failure. Changes in $\dot{V}_{ADS}$ may result from a change in ventilatory pattern, but the V_T/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 $\dot{V}_E/\dot{V}_{CO_2}$ slope in normal controls.[15] Rather than the increase in $\dot{V}_{ADS}$ leading to an increased $\dot{V}_E/\dot{V}_{CO_2}$ 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.

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