

# Pattern of ventilation during exercise in chronic heart failure

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Heart 2003;89:610–614

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Accepted  
19 February 2003

**Objective:** To determine the pattern of the abnormal ventilatory response in heart failure and how it relates to symptoms by looking at tidal volume ( $V_T$ ) and frequency ( $f$ ) during exercise.

**Methods:** 45 patients with heart failure and 21 controls underwent maximal treadmill based exercise testing with metabolic gas exchange analysis. The relation of ventilation ( $\dot{V}_E$ ) to  $V_T$  was plotted to look for an inflection point where  $V_T$  failed to increase further. The slope of the relation before this inflection point was documented. Time to the inflection point,  $V_T$ , and  $f$  at the inflection point were recorded. The relation of symptom scores to  $f$  and  $\dot{V}_E$  was also examined.

**Results:** Peak oxygen consumption ( $\dot{V}O_{2p}$ ) (mean (SD)) was lower (19.7 (4.5) v 37.9 (8.6) ml/kg/min;  $p < 0.001$ ) and the ventilation to carbon dioxide production ( $\dot{V}_E/\dot{V}CO_2$ ) slope was steeper (40.0 (6.5) v 26.0 (1.6);  $p < 0.0001$ ) in patients with heart failure than in the control group. The patients reached the inflection point of the  $\dot{V}_E/V_T$  slope sooner during exercise than the controls (271 (110) v 502 (196) seconds;  $p < 0.0001$ ). Patients had a higher  $f$  and a smaller  $V_T$  at that point and throughout exercise until the peak where  $f$  was the same for patients and controls.  $V_T$  at the inflection point correlated with  $\dot{V}O_{2p}$  ( $r = 0.67$ ;  $p < 0.0001$ ). Despite having an increased sensation of breathlessness for a given  $\dot{V}_E$ , patients were less symptomatic of  $f$  than controls.

**Conclusions:** Patients with heart failure breathe at a higher  $f$  throughout exercise, reaching an apparent maximal  $V_T$  earlier. The  $V_T$  at an inflection point on the  $\dot{V}_E/V_T$  slope predicts  $\dot{V}O_{2p}$ .

The dominant symptom of patients with treated chronic heart failure is exercise intolerance, usually caused by breathlessness and fatigue. This can be assessed objectively by incremental exercise testing with metabolic gas exchange measurements to derive peak oxygen consumption ( $\dot{V}O_{2p}$ ) as an index of exercise capacity.<sup>1</sup> At the same time, the slope of the relation between ventilation and carbon dioxide production ( $\dot{V}_E/\dot{V}CO_2$  slope) can be used to characterise the ventilatory response to exercise.<sup>2,3</sup> Typically in chronic heart failure,  $\dot{V}O_{2p}$  is reduced and the  $\dot{V}_E/\dot{V}CO_2$  slope is increased.<sup>4,5</sup> Thus, for a given  $\dot{V}CO_2$ , the ventilatory response ( $\dot{V}_E$ ) is greater.  $\dot{V}O_{2p}$  and  $\dot{V}_E/\dot{V}CO_2$  vary inversely and both are related to symptom scores and prognosis.<sup>6,7</sup>

$\dot{V}_E$  is the product of tidal volume ( $V_T$ ) and breathing frequency ( $f$ ), and a varying combination of the two variables can generate an increase in  $\dot{V}_E$  during exercise. Previous investigators have suggested that there is an increase in  $f$  for a given  $V_T$ .<sup>8</sup> This has the potential effect of increasing dead space ventilation; at a given  $\dot{V}_E$ , if  $f$  is increased and therefore  $V_T$  is reduced, then fixed anatomical dead space is ventilated more often and forms a higher proportion of  $\dot{V}_E$ . Yokohama and colleagues<sup>9</sup> previously reported that  $f$  starts to increase relative to  $V_T$  simultaneously with the perception of breathlessness, although this has not been replicated.<sup>10</sup>

We wished to characterise more closely the ventilatory response to exercise looking particularly at the relation of  $f$  and  $V_T$  to total minute ventilation and  $\dot{V}CO_2$ , and their relation to exercise capacity and the perception of breathlessness.

## PATIENTS AND METHODS

We examined the responses to exercise of 45 consecutive patients with chronic heart failure and 21 controls. The control group consisted of age matched subjects chosen at random from the lists of local general practitioners. The study was approved by the local ethics committee.

Chronic heart failure was defined as the presence of symptoms of fatigue or breathlessness on exertion and a left

ventricular ejection fraction on echocardiography of  $< 40\%$  with no other apparent cause of breathlessness. The condition had to be of at least three months' duration with no recent exacerbation or change in medication. Patients with evidence of symptomatic chest disease, neurological conditions, or inducible ischaemia were excluded from the analysis. We also excluded patients and controls with a forced expiratory volume in one second ( $FEV_1$ ) of  $< 75\%$  of the predicted volume. None of the control subjects was taking regular medication and all underwent echocardiography to exclude left ventricular dysfunction.

Each subject underwent symptom limited treadmill based maximal exercise testing using a Bruce protocol modified by the addition of a "stage 0" at onset consisting of three minutes of exercise at 1.61 km/hour (1 mile/hour) with a 5% gradient. Participants were encouraged to exercise to exhaustion. During the tests patients wore a tightly fitting face mask to which was connected a capnograph and a sample tube enabling online measurement of ventilation and metabolic gas exchange (Oxycon Delta system, Jaeger, Hoechberg, Germany). A respiratory exchange ratio ( $\dot{V}CO_2/\dot{V}O_2$ )  $> 1$  was taken to suggest a maximal effort. Spirometry ( $FEV_1$  and forced vital capacity) was performed before the exercise test. At the end of each stage and at peak exercise subjects were asked to indicate their score for dyspnoea or fatigue on a scale from 0 (no symptoms) to 10 (maximal symptoms) using a standardised scoring system.<sup>11</sup> The anaerobic threshold was calculated by the V slope method.<sup>12</sup>

**Abbreviations:**  $f$ , frequency of ventilation;  $FEV_1$ , forced expiratory volume in one second;  $\dot{V}O_{2p}$ , peak oxygen consumption; NYHA, New York Heart Association;  $\dot{V}CO_2$ , carbon dioxide production;  $\dot{V}_E$ , minute ventilation;  $\dot{V}_E/\dot{V}CO_2$ , ventilatory equivalent of carbon dioxide;  $V_T$ , tidal volume

**Table 1** Subject characteristics

	Patients (n=45)	Controls (n=21)	p Value
Age (years)	69 (9.6)	66 (8.1)	0.18
Height (cm)	171 (6.9)	175 (6.9)	0.06
Weight (kg)	78.6 (13.5)	79.7 (10.5)	0.74
FEV <sub>1</sub> (% expected)	90.0 (17.4)	116.0 (23.4)	<0.0001
FVC (% expected)	80.0 (22.9)	95.0 (22.6)	0.0001
Sex (male:female)	41:4	18:3	
LVEDD (cm)	6.5 (0.7)	5.0 (0.6)	<0.0001
LVEF (%)	33.6 (5.4)	61.0 (9.9)	<0.0001
Drugs			
Furosemide (mean daily dose)	83.4 (53.4)		
β Blockers (n)	15		
ACEI/AlIA (n)	44		
Spirolactone (n)	21		
New York Heart Association (functional class n)			
II	27		
III	18		
$\dot{V}O_2$ (ml/kg/min)	19.7 (4.5)	37.9 (8.6)	<0.0001
Exercise time (s)	420 (132)	817 (208)	<0.0001
Anaerobic threshold (ml/kg/min)	14.3 (3.7)	28.4 (8.4)	<0.0001
RER	1.05 (0.06)	1.05 (0.07)	0.92
Borg/ $\dot{V}E$ slope	0.176 (0.04)	0.123 (0.07)	0.001
$\dot{V}E/\dot{V}CO_2$ slope	40.0 (6.5)	26.0 (1.6)	<0.0001

Values are means (SD).

ACEI, angiotensin converting enzyme inhibitor; AlIA, angiotensin II inhibitor; FEV<sub>1</sub>, forced expiratory volume in one second; FVC, forced ventilatory capacity; LVEDD, left ventricular end diastolic dimension from M mode echocardiography; LVEF, ejection fraction (%);  $\dot{V}O_2$ , peak oxygen consumption; RER, respiratory exchange ratio (carbon dioxide production to oxygen consumption ( $\dot{V}CO_2/\dot{V}O_2$ ));  $\dot{V}E$ , ventilatory response.

To allow construction of a slope relating symptom scores to total ventilation, we included only patients who managed at least the first stage (stage 0) of the protocol outlined above.

We plotted  $V_T$  against  $f$  ( $V_T/f$  slope) and  $V_T$  against  $\dot{V}E$  ( $\dot{V}E/V_T$  slope) for exercise in all subjects. Any inflection point on each slope was identified by a single reporter (KW), and  $\dot{V}E$ ,  $V_T$ ,  $f$ , oxygen consumption, and the ventilatory equivalent of carbon dioxide ( $\dot{V}E/\dot{V}CO_2$ ) at that point were documented. Specifically, the inflection point on the slope relating  $\dot{V}E$  to  $V_T$  was identified by plotting a simple regression slope at the proximal results (early exercise) and one for the later stages of exercise similar to the  $V$  slope method for the identification of the anaerobic threshold.<sup>12</sup> The average Borg score,  $\dot{V}E$ , and  $f$  at the end of each stage for controls and patients were plotted against each other to derive slopes for  $\dot{V}E/\text{Borg}$  and  $f/\text{Borg}$  relations. The  $\dot{V}E/\text{Borg}$  slope was also calculated for each person. These individual data were compared using unpaired Student's  $t$  test. The reporter was blinded as to the identity of the subjects and whether they were patients or controls.  $\dot{V}E/\dot{V}CO_2$  was recorded at rest, at the anaerobic threshold, and at peak exercise. Maximum voluntary ventilation was calculated as  $35 \times \text{FEV}_1$ .<sup>13</sup>

Results are reported as mean (SD). We used an unpaired Student's  $t$  test for between group comparisons. A probability value of  $p < 0.05$  was taken to suggest that the observed differences between the control population and the patients were significant. We performed linear regression analysis to explore the relation between variables.

**Table 2** Variables at peak exercise

	Patients (n=45)	Controls (n=21)	p Value
$\dot{V}E$ peak (l/min)	65.7 (13.5)	89.9 (22.5)	<0.0001
$V_T$ (l)	1.8 (0.4)	2.6 (0.6)	<0.0001
$f$ (breaths/min)	38.1 (6.8)	35.2 (6.4)	0.1
Heart rate (beats/min)	126 (25)	162 (20)	<0.0001
%MVV	78.3 (12.8)	78.9 (13.3)	0.86

Values are means (SD).

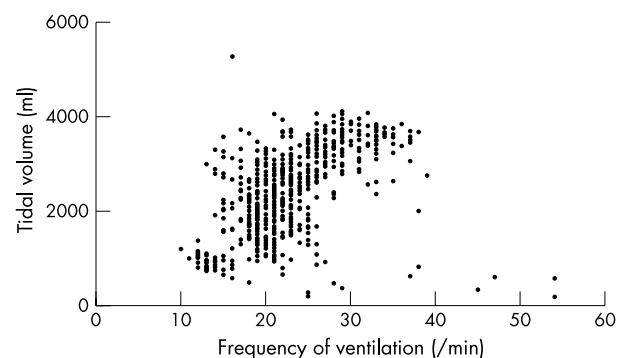
$f$ , frequency of ventilation; MVV, maximal voluntary ventilation;  $V_T$ , tidal volume.

## RESULTS

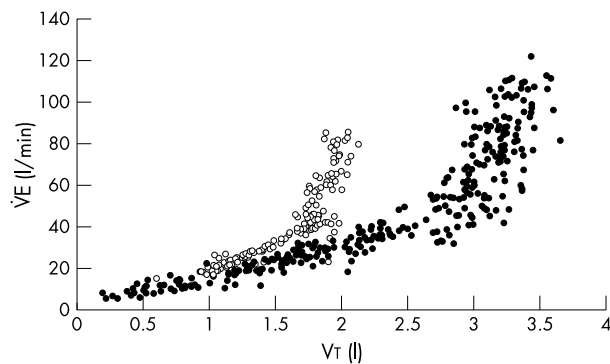
Table 1 shows characteristics of the study groups. All patients but one were taking angiotensin converting enzyme inhibitors or angiotensin II inhibitors, and 15 were taking  $\beta$  blockers.  $\dot{V}O_2$ , anaerobic threshold, and exercise time were greater in the controls than in the patients. The respiratory exchange ratio at peak exercise was the same in both groups suggesting similar levels of exertion. The  $\dot{V}E/\dot{V}CO_2$  slope was steeper in the patients than in the controls. At peak exercise  $f$  was not significantly different between the two groups. However, total minute ventilation was significantly less in the patients because of a lower  $V_T$  (1.8 (0.4) v 2.6 (0.6);  $p < 0.0001$ ) (table 2).  $\dot{V}E/\dot{V}CO_2$  and the ventilatory equivalent for oxygen were also significantly higher at peak in the patients.

Although patients with specific lung pathology or reduced lung function were excluded from the analysis, both forced vital capacity and FEV<sub>1</sub> were reduced in patients (table 1).

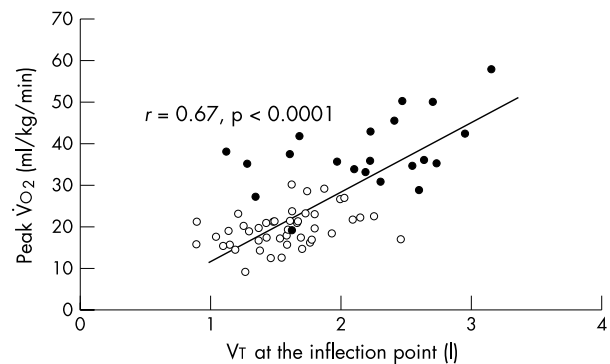
We could describe an inflection point in the  $V_T/f$  relation in only six patients and seven control subjects (fig 1). However, in all subjects an inflection point was identified in the  $\dot{V}E/V_T$  relation at which  $V_T$  no longer increased significantly with the slope becoming almost perpendicular to the x axis (fig 2). Total ventilation at this point was the same in patients and controls (44.6 (10.8) v 40.0 (14.5) l/min;  $p = 0.2$ ), but  $f$  was



**Figure 1** Relation of tidal volume ( $V_T$ ) to frequency ( $f$ ) during a peak exercise test in a typical control subject. No inflection point can be observed.



**Figure 2** Relation of minute ventilation ( $\dot{V}_E$ ) to tidal volume ( $V_T$ ) during a peak exercise test in a typical patient (open circles) and a control subject (closed circles). An inflection point can be observed for both subjects.



**Figure 3** Relation between  $V_T$  at the inflection point and the peak oxygen consumption ( $\dot{V}O_2$ ) at the inflection point for patients (open circles) and controls (closed circles).

**Table 3** Values at the inflection point

	Patients (n=45)	Controls (n=21)	p Value
Time to inflection (s)	271 (110)	502 (196)	<0.0001
$V_T$ (l)	1.6 (0.3)	2.2 (0.6)	0.0001
$f$ (breaths/min)	25.8 (5.8)	20.7 (3.8)	0.0004
$\dot{V}_E$ (l/min)	40.0 (14.5)	44.6 (10.8)	0.2
$\dot{V}_E$ as % peak $\dot{V}_E$	61.6 (14.4)	50.5 (12.8)	<0.004
$\dot{V}_E$ as %MVV	47.7 (11.8)	39.0 (8.6)	0.003
$\dot{V}_E/V_T$ slope before IP	21.6 (6.8)	15.8 (4.1)	0.0007
$\dot{V}_{eqO_2}$	33.1 (6.6)	19.9 (2.2)	<0.0001
$\dot{V}_{eqCO_2}$	38.1 (5.4)	24.8 (2.7)	<0.0001
$\dot{V}O_2$ (ml/kg/min)	15.1 (3.5)	26.9 (7.3)	<0.0001
Borg score	3.7 (2.2)	2.8 (1.7)	0.1

Values are means (SD).

\*IP, inflection point;  $\dot{V}_{eqCO_2}$ , ventilatory equivalent for carbon dioxide;  $\dot{V}_{eqO_2}$ , ventilatory equivalent for oxygen.

greater (25.8 (5.8)  $\nu$  20.7 (3.8) l/min;  $p = 0.0004$ ) and  $V_T$  smaller in patients (1.6 (0.3)  $\nu$  2.2 (0.6) l;  $p < 0.0001$ ). Oxygen consumption at the inflection point was lower and the ventilatory equivalents for the metabolic gases were greater at the inflection point in the patients than in the controls, as was the Borg score (table 3). The patients were also breathing at a greater percentage of their maximum voluntary ventilation capacity and at a greater proportion of peak ventilation at the inflection point.

The gradient of the  $\dot{V}_E/V_T$  slope before the inflection point was significantly steeper in patients than in controls (fig 2)

(21.6 (6.8)  $\nu$  15.8 (4.1);  $p = 0.0007$ ) so that at a given  $\dot{V}_E$ ,  $V_T$  was smaller. This slope correlated with the  $\dot{V}_E/\dot{V}CO_2$  slope ( $r = -0.42$ ;  $p = 0.0004$ ). The patients reached the inflection point significantly sooner than did the controls (271  $\nu$  502 seconds;  $p < 0.0001$ ).  $V_T$  at the inflection point predicted  $P\dot{V}O_2$  ( $r = 0.67$ ;  $p < 0.0001$ ) (fig 3). This relation remained significant within the patient group ( $r = 0.37$ ;  $p < 0.001$ ).

Within the patient group, there were significant differences in the exercise variables between patients in New York Heart Association (NYHA) functional classes II and III (table 4). The  $P\dot{V}O_2$  was lower and the  $\dot{V}_E/\dot{V}CO_2$  slope steeper in those in class III. There were no significant differences in  $FEV_1$  and forced vital capacity between the classes, or in  $V_T$ ,  $\dot{V}_E$ , and  $f$  at peak exercise. Patients in NYHA class III reached the inflection point significantly sooner than those in class II ( $p < 0.05$ ). The ventilatory variables were otherwise not significantly different at the inflection point (table 4).

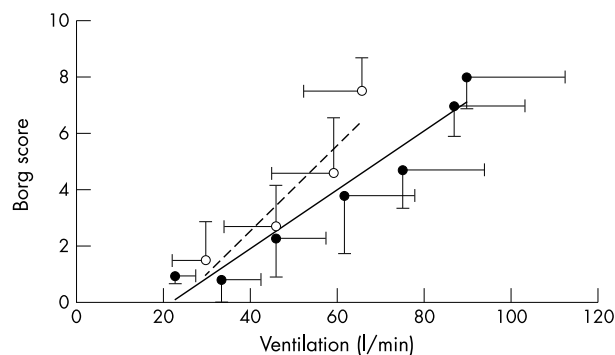
Patients were more symptomatic for a given level of ventilation from the outset of exercise shown by a steeper slope relating  $\dot{V}_E$  to Borg score (0.176 (0.04)  $\nu$  0.123 (0.07);  $p = 0.001$ ) (fig 4). The Borg/ $\dot{V}_E$  slope correlated with  $P\dot{V}O_2$  ( $r = 0.52$ ;  $p < 0.0001$ ). However, the slope relating Borg score to  $f$  was not greater in patients than controls (0.47 (0.03)  $\nu$  0.45 (0.05);  $p = 0.4$ ) but was shifted to the right (fig 5). Patients in class III had significantly steeper Borg/ $\dot{V}_E$  slopes than those in class II (fig 6).

## DISCUSSION

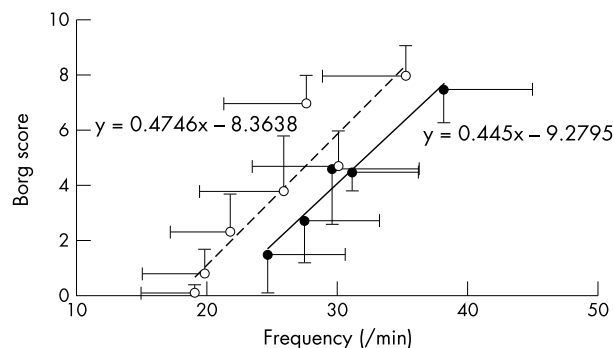
$\dot{V}_E$  increases during exercise. Total minute ventilation is the product of  $V_T$  and  $f$ , and during exercise both increase to generate a rise in  $\dot{V}_E$ . Any pair of lungs must, however, reach a

**Table 4** Ventilatory variables in patients according to New York Heart Association (NYHA) functional class

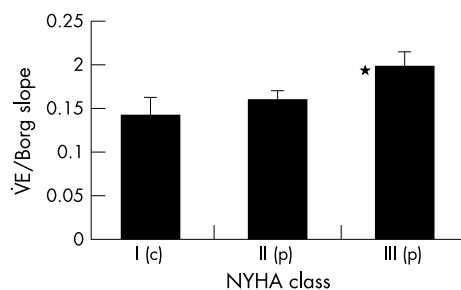
	NYHA II (n=27)	NYHA III (n=18)	p Value
$FEV_1$ (% expected)	2.42 (0.4)	2.42 (0.5)	0.98
FVC(% expected)	3.21 (0.7)	3.05 (0.7)	0.50
Sex (male:female)	41:4	18:3	
LVEDD (cm)	6.5 (0.8)	6.6 (0.9)	0.65
LVEF (%)	34.0 (5.4)	33.1 (5.5)	0.71
$P\dot{V}O_2$ (ml/kg/min)	20.8 (4.7)	18.0 (3.6)	0.19
Exercise time (s)	456 (140)	367 (100)	<0.05
Anaerobic threshold (ml/kg/min)	15.3 (3.9)	12.8 (2.7)	0.15
RER	1.05 (0.06)	1.05 (0.06)	0.86
$\dot{V}_E/\dot{V}CO_2$ slope	38.3 (5.1)	42.5 (7.7)	<0.05
Borg/ $\dot{V}_E$ slope	0.16 (0.06)	0.2 (0.07)	<0.05
$\dot{V}_E$ peak (l/min)	66.0 (13.2)	65.4 (14.2)	0.90
$V_T$ peak (l)	1.8 (0.4)	1.7 (0.3)	0.38
$f$ peak (breaths/min)	37.3 (6.5)	39.3 (7.1)	0.33
Time to IP (s)	301 (110)	225 (95)	<0.05



**Figure 4** Relation between the Borg score and averaged minute ventilation for each stage during a peak exercise test in patients (dashed line) and controls (solid line). The error bars represent standard deviations around the means.



**Figure 5** Relation between the Borg score and averaged  $f$  (standard deviations are shown) for patients (dashed line) and controls (solid line). The error bars represent the standard deviations around the means.



**Figure 6** Mean  $\dot{V}E/Borg$  slope according to New York Heart Association functional class (p, patient; c, control; \* $p < 0.05$  between those in class II and class III). The error bars represent the standard deviation around the means.

limit of  $V_T$  past which further increases in  $\dot{V}E$  depend on increases in  $f$ . This occurs in the later stages of exercise.

Patients with chronic heart failure ventilate more during exercise than controls,<sup>14</sup> resulting in an increase in the  $\dot{V}E/\dot{V}CO_2$  slope.<sup>4,5</sup> Previous work has shown that patients breathe at a lower  $V_T$  and higher  $f$  throughout exercise.<sup>8</sup> The reason for this remains unclear but may lead to an increase in the proportion of dead space ventilation. The increased  $\dot{V}E/\dot{V}CO_2$  slope would be a consequence.<sup>8</sup> However, the volume of dead space as a proportion of total ventilation is the same in patients and controls during exercise.<sup>15</sup> The increased  $\dot{V}E/\dot{V}CO_2$  slope must therefore be a result of other mechanisms. Ventilation perfusion mismatch,<sup>16–18</sup> impaired diffusion of metabolic gases,<sup>19</sup> respiratory muscle weakness,<sup>20,21</sup> and heightened sensitivity of peripheral receptors<sup>22–24</sup> have all been postulated as possible causes.

Yokoyama and colleagues<sup>9</sup> reported a point on the  $V_T/f$  curve at which  $f$  started to increase relative to  $V_T$  and that it was at this point that symptom scores rose. Dimopoulou and colleagues<sup>25</sup> also plotted the slope relating  $V_T$  to  $f$  in patients with chronic heart failure but were able to identify an inflection point on only 73%. Neither group reported data from controls. In our subjects we were unable to identify such a point reliably and therefore used the slope of  $V_T$  against  $\dot{V}E$  to identify the contribution of each component to total ventilation. This showed a clear inflection point where  $f$  increases more rapidly and  $V_T$  fails to increase further, which may be unequivocally identified in all subjects. Before this, the  $V_T/\dot{V}E$  slope is significantly steeper for patients than for controls. This implies that patients depend more on increases in  $f$  to mediate increases in  $\dot{V}E$  than controls from the outset of exercise. Patients with heart failure have respiratory muscle weakness.<sup>20,21</sup> Rapid shallow breathing has a lower energetic cost than deep breathing<sup>26</sup> but is less efficient in terms of alveolar ventilation because of the relative increase in dead space ventilation. This breathing pattern may occur after inspiratory muscle fatigue to minimise respiratory sensation.<sup>27</sup>

Although  $f$  during exercise is greater in patients, at peak exercise  $f$  is the same for patients of both NYHA classes and controls despite significantly lower peak  $\dot{V}E$  in the patients. As a consequence  $V_T$  at peak determines the maximum  $\dot{V}E$  achieved.

Previous data have suggested that  $\dot{V}E$  does not limit peak exercise in patients with heart failure.<sup>28,29</sup> In the present study, however,  $V_T$  at an early point predicted  $P\dot{V}O_2$ . This influence of  $V_T$  on exercise capacity is important because it may partly explain the benefit from positive pressure ventilation,<sup>30</sup> which may improve the depth of breathing and help in training programmes aimed at improving the control and depth of ventilation.<sup>31</sup> Furthermore, recent work showing the presence of increased resistance to airflow and reduced lung compliance in patients with chronic heart failure confirms the importance of pulmonary function and the work of breathing on symptoms in chronic heart failure.<sup>32</sup>

The present study also showed that patients and controls ventilate at the same proportion of maximum voluntary ventilation at peak. As this measure is recorded at rest this suggests that the likely defect of ventilatory mechanics is present during rest and exercise. Several authors have found impaired inspiratory muscle strength<sup>33–35</sup> and endurance.<sup>36</sup>

We also observed that the patients were more symptomatic for a given level of ventilation and that this was related to their NYHA status. The slope relating  $f$  to Borg score was shifted to the right, giving a higher  $f$  for a given symptom score. The slope was, however, the same for patients and controls. This, and the fact that  $f$  is the same at peak in both groups, implies that  $f$  is not the cause of increased symptoms in patients with heart failure, as suggested by previous work.<sup>9</sup> The present study actually suggests that patients are less symptomatic for a given  $f$  than are controls.

In conclusion, we have shown reduced  $V_T$  throughout exercise, that this is closely linked with exercise performance, and that ventilation is initially maintained by an increase in  $f$ , which may later in exercise contribute to fatigue of respiratory muscles. The present study also shows that  $V_T$  at an inflection point occurring early in exercise predicts  $P\dot{V}O_2$ . The cause of the impairment in  $V_T$  remains to be elucidated but it is possible that this “peak  $V_T$ ” may be a method of assessing outcome in patients unable to perform a true peak exercise test. These abnormalities in the pattern of ventilation seem to worsen with increasing severity of heart failure. Patients are more symptomatic for a given ventilation but this seems not to be caused by the increased  $f$ .

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