Increased exercise ventilation in patients with chronic heart failure: intact ventilatory control despite hemodynamic and pulmonary abnormalities

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ABSTRACT This study was designed to determine the pathophysiologic basis of increased exercise ventilation in the presence of chronic heart failure. Sixty-four ambulatory patients with chronic heart failure and 38 age-matched normal control subjects performed exercise according to identical staged, symptom-limited bicycle exercise protocols with measurement of hemodynamic, ventilatory, and metabolic responses. Compared with normal subjects, ventilation and the ratio of ventilation to CO₂ production (Ve/VCO₂), and pulmonary capillary wedge pressure were elevated in patients at rest and during exercise. The ratio of pulmonary dead space to tidal volume (Vd/Vt) also was elevated in the heart failure group at rest and during exercise and was closely related to Ve/VCO₂ (all r > .72, p < .001). Rest and exercise arterial PCO₂ regulation was normal in patients. Peak exercise Ve/VCO₂ did not correlate with pulmonary vascular pressures, but was inversely related to cardiac output (r = -.49, p < .001). Thus, neurohumoral ventilatory control mechanisms are intact in patients with chronic heart failure and act to maintain normal Paco₂ levels in the face of increased pulmonary dead space. Activation of abnormal reflexes due to hemodynamic derangements during exercise are not important in determining ventilation in the presence of chronic heart failure. The demonstration of a correlation between decreased cardiac output and increased ventilation in the patient group suggests that attenuated pulmonary perfusion may play a role in causing exercise hyperpnea in the presence of chronic heart failure by producing ventilation perfusion abnormalities and thereby increasing physiologic pulmonary dead space.


IN PATIENTS who present with acute pulmonary edema, a rapid elevation in pulmonary capillary wedge pressure leads to interstitial fluid accumulation, decreased lung compliance, and obstructive airway physiology,¹ ² and is the primary factor causing dyspnea. However, the role of increased intrapulmonary vascular pressures in causing ventilatory abnormalities and dyspnea in stable ambulatory patients with chronic heart failure has not been clearly defined. Studies in patients with mainly valvular heart disease have emphasized the importance of elevated pulmonary capillary wedge pressures during exercise in causing dyspnea by decreasing lung compliance³-⁵ and stimulating pulmonary juxtaglomerular receptors⁶-⁸ leading to a hyperventilation response.³ ⁷ ⁸ However, recent investigations have been unable to demonstrate a direct link between exertional breathlessness and pulmonary capillary wedge pressure.⁹ ¹⁰ Numerous studies have consistently identified a heightened ventilatory response to exercise in heart failure, which may be an important factor causing exertional dyspnea.⁷ ¹¹ ⁻¹⁷ The pathophysiologic basis for this increased ventilation during exercise has not been fully characterized. Several underlying mechanisms have been suggested, including early lactic acidosis,¹³ ¹⁵ coexisting pulmonary disease with increased pulmonary dead space,¹¹ ¹³ ¹⁴ an abnormal respiratory pattern with rapid shallow ventilation,¹⁵ increased pulmonary capillary wedge pressures with reflex hyperventilation,³ ⁵ ¹⁷ altered arterial PCO₂ control,¹⁴ and skeletal muscle acidosis.¹⁷

The present study was designed to determine the hemodynamic, metabolic, and pulmonary factors associated with the increased ventilatory drive in conges-
tive heart failure and the relationship between peak exercise ventilatory drive and exertional dyspnea. To determine these relationships, 64 patients with chronic heart failure underwent maximal bicycle exercise testing with expired gas analysis and hemodynamic monitoring. The data from this group were compared with those derived from identical hemodynamic exercise testing in 38 age-matched normal volunteers to clearly define abnormal hemodynamic and ventilatory exercise responses.

Methods

Patient population. Sixty-two men and two women with heart failure due to left ventricular dysfunction participated in the study. The New York Heart Association functional classifications were as follows: two patients were in class I, 32 patients were in class II, 27 patients were in class III, and three patients were in class IV. All patients were clinically stable for 1 month before the study. Left ventricular ejection fraction was 20 ± 6% (range 11% to 36%) by radionuclide angiography. Eight patients had mild pedal edema, but none had pulmonary rales at the time of study. Exercise was limited by dyspnea or fatigue in all patients. No patient had pulmonary disease by history, chest x-ray, or physical examination. All patients were taking diuretics and 44 were receiving digoxin. Seven subjects were receiving angiotensin converting–enzyme inhibitors. Results of routine pulmonary spirometry were available in 34 patients.

Normal subjects. Thirty-eight men with a normal medical history and physical examination who were on no medications volunteered to serve as control subjects. All had a normal electrocardiographic response on a screening maximal bicycle exercise test. Only four subjects were engaged in regular aerobic exercise and eight were cigarette smokers.

Exercise protocol. All studies were performed under a research protocol approved by the Institutional Review Boards of both the Duke University and the Durham Veterans Administration Medical Centers. Subjects underwent a familiarization maximal exercise test with expired gas analysis 2 to 14 days before the study. Patients were given their usual cardiac medications 3 hr before testing, which was usually at 10:00 A.M. All subjects underwent maximal bicycle exercise (Fitron Isokinetic Bicycle, Lumex, Inc.) at least 2 hr postprandially with expired gas analysis and hemodynamic monitoring. Exercise began at 150 kilopond-meters (kpm)/min and was advanced 150 kpm/min in 3 min stages to a symptom-limited maximum for each exercise study. Heart rate was monitored by standard electrocardiographic leads and blood pressure was measured by sphygmomanometer or direct intra-arterial pressure recording.

Expired gas analysis. For the first 14 normal subjects and the first 20 patients expired oxygen was analyzed continuously with a Beckman OM-14 oxygen analyzer, carbon dioxide by a Beckman LB-2 analyzer, and minute ventilation with a Pneumoscan spirometer. In the remaining subjects a Sensormedics 2000 breath-by-breath analysis unit was used. Each system introduces a low volume of dead space to the ventilatory circuit and was calibrated before each study. Expired gases were analyzed in patients at equilibrated upright rest on the bicycle and continuously during exercise. Averaged measurements from the last 30 sec of each exercise stage were used for analysis.

Hemodynamics. All patients and 22 normal control subjects had a No. 7F Swan-Ganz catheter positioned in the right pulmonary artery via an antecubital vein, and a 2 inch cannula placed in the brachial artery 1 hr before exercise. Pulmonary and systemic arterial pressures were recorded continuously and pulmonary capillary wedge pressure was recorded intermittently at rest and at each workload with Hewlett-Packard transducers, amplifiers, and recorders, as previously described in our laboratory. At rest and in the third minute of each workload, arterial and mixed venous blood was drawn for oximetry (Instruments Laboratory Model 282) to determine Fick cardiac outputs. Lactate concentration was determined in arterial blood samples (Calbiochem-Behring rapid lactate kit). In eight normal subjects and 18 patients arterial and mixed venous blood was also drawn at rest and at each workload for measurement of PO₂, PCO₂, and pH (Instruments Laboratory Model 1303).

Reproducibility studies. To determine the reproducibility of ventilatory measurements and the effects of catheterization on rest and exercise oxygen consumption (VO₂), ventilation (Ve), respiratory exchange ratio, CO₂ production (VCO₂), and the ratio of ventilation to VCO₂ (Ve/VCO₂), five patients with heart failure underwent a third noninvasive maximal exercise study within 1 month of the hemodynamic study.

Derived variables. Ve/VCO₂ was used as an index of ventilatory drive, since it has previously been demonstrated that CO₂ production is the primary metabolic stimulus for Ve in normal man and in patients with heart failure. The ratio of pulmonary dead space to tidal volume (Vd/Vt) was derived from the modified alveolar gas equation:

\[
Ve = 863 \times \frac{VCO_2}{(Paco_2 \times (1 - Vd/Vt))}
\]

Effective alveolar ventilation (VA) was derived from the equation:

\[
VA = Ve \times (1 - Vd/Vt)
\]

The ratio of VA to VCO₂ (VA/VCO₂) was used as an index of ventilatory drive that is independent of individual variations in Vd/Vt. Total dead space per breath (Vd/Br) is composed of both anatomic (airway) and physiologic pulmonary dead space. Since anatomic dead space would not likely be different in the two groups, this variable was used to reflect physiologic dead space and was calculated as follows:

\[
Vd/Br = Vt \times Vd/Vt
\]

Statistical approach. To define abnormal exercise responses in the patients, variables for this group were compared with those in the normal subjects. Group comparisons were made by use of paired and unpaired Student’s t tests where appropriate. To determine the relationships of hemodynamic, metabolic, and pulmonary factors to the ventilatory response within the patient group, linear and multivariate regression analyses were performed. When multiple correlations were performed a Bonferroni adjustment was used; otherwise a value of p < .05 was considered indicative of a significant difference. All data are reported as the mean ± SD.

Results

Reproducibility studies. There were no differences between corresponding resting or exercise values for any of the ventilatory variables from the two studies. The correlation coefficients and standard errors of the estimate from the derived regression equations of paired resting and exercise values from the invasive and additional noninvasive studies were as follows: VO₂ r = .90, p < .001, SEE = 81 ml; Ve r = .95, p < .001, SEE = 6.4 liters/min; respiratory exchange ratio r = .89, p < .001, SEE = .08; VCO₂ r = .97, p < .001, SEE = 132 ml; Ve/VCO₂ r = .85, p < .001, SEE =
4.3. Thus, resting, submaximal, and maximal ventilatory variables were not altered by hemodynamic monitoring and exhibited good day-to-day reproducibility.

**Group characteristics.** There was no difference in age between the patients (55 ± 10 years, range 34 to 74) and the normal subjects (52 ± 13 years, range 27 to 76). The normal subjects were slightly heavier (82 ± 11 vs 78 ± 14 kg) than the patients (p = .03). Body surface area showed no intergroup difference and was 1.90 ± 0.11 m² in normal subjects and 1.87 ± 0.18 m² in the patients. Forced vital capacity, forced expiratory volume at 1 sec (FEV₁), and maximal voluntary ventilation were all approximately 75% of the predicted value in the patient group (table 1).

**Expired gas analysis.** Respiratory exchange ratio at peak exercise was 1.25 ± 0.15 in the patients and 1.28 ± 0.13 in the normal group, indicating maximal or near-maximal exertion in the two groups. Peak VO₂ was 15.1 ± 4.1 ml/kg/min (1.16 ± 0.31 liters/min) in the patients, and 26.4 ± 8.0 ml/kg/min (2.16 ± 0.56 liters/min) in the normal group (p < .001; figure 1, A). To compare the groups at matched workloads, results from 150 and 300 kpm/min stages were compared since these were submaximal for 59 patients and all controls. Resting and submaximal exercise VO₂ were similar in the two groups. There were no intergroup differences in VCO₂ at rest or 150 kpm/min, while VCO₂ tended to be higher in the patients at 300 kpm/min (p = .06; figure 1, B). The change in VCO₂ from rest to 300 kpm/min was 621 ± 145 ml/min in patients and 552 ± 133 ml/min in normal subjects (p = .02). Maximal VCO₂ in the normal group was almost double that seen in patients, reflecting attainment of a higher work rate. The patients demonstrated increased ventilation at rest and submaximal exercise, while the peak value was only 63% of the normal maximum (figure 1, C).

The Ve/VCO₂ ratio was significantly higher in the patient group at rest and submaximal and maximal exercise compared with that in the normal group (figure 1, D). At rest, tidal volume (VT) (figure 1, E) was slightly lower in patients (p = .04). However, submaximal exercise VT was nearly identical in the two groups. Peak exercise VT was 63% of the normal peak value in the patient group, but when adjusted for workload, it was normal. The respiratory rate (figure 1, F) was increased at rest and during submaximal exercise in the patient group but at peak exercise it was no different in the two groups.

Rest and exercise Vd/VT were significantly elevated in the patient group (figure 2, A). At rest, the total Vd/Br (figure 2, B) was not significantly different from normal in the patient group (p = .18). Vd/Br was elevated in the patients during submaximal exercise compared with that in control subjects and was markedly increased at peak exercise. The change in Vd/Br from rest to maximal exercise, which primarily reflects changes in physiologic dead space, was 0.19 ± 0.15 liter in patients vs 0.02 ± 0.16 liter in normal subjects (p < .05). Effective VA was similar in the two groups.
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FIGURE 3. Resting and exercise arterial and mixed venous PO2, PCO2, and pH in patients with chronic heart failure (solid bars) and normal subjects (open bars). Bars represent mean ± SD. *p < .05 patients vs normal subjects; **p < .001 patients vs normal subjects.

at rest and submaximal exercise (figure 2, C), although the value at maximal exercise was only 38% of normal in patients. The VA/VCO2 ratio (figure 2, D) was comparable in the two groups at rest and during exercise. VA/VCO2 was remarkably constant at rest and submaximal exercise in the two groups, but increased from rest to maximal exercise in both groups (both p < .05).

Arterial blood gases. PaO2 (figure 3, A) was lower in the patient group at rest but increased to normal levels at maximal exercise. SaO2 was greater than 90% in all patients at rest and during exercise and did not differ at rest or during exercise in the two groups. Mixed venous PO2 (figure 3, B) was decreased in patients at rest and during submaximal exercise. There was no intergroup difference in this value at maximal exercise. Resting and submaximal and maximal exercise PacO2 were not different in the two groups (figure 3, C), although maximal PacO2 tended to be slightly lower in normal subjects at peak exercise. At rest, mixed venous PCO2 (figure 3, D) was normal in patients but increased at a faster rate during submaximal exercise, reaching a peak exercise value that was comparable to the normal value. Arterial pH (figure 3, E) tended to be slightly higher in the heart failure group at rest, although this difference did not reach statistical significance (p = .14). Arterial pH was significantly higher in the patient group compared with control subjects during all exercise stages. Mixed venous pH was not different at rest or submaximal or maximal exercise in the two groups (figure 3, F).

Hemodynamic and lactate response. Cardiac output was reduced in the patient group (figure 4, A) at rest and at all exercise workloads. Mean pulmonary artery pressure (figure 4, B) and pulmonary capillary wedge pressure (figure 4, C) were elevated at rest and during exercise in the patient group. Arterial lactate (figure 4, D) was similar in the two groups at rest but increased more rapidly in the patient group during exercise. This is consistent with previous studies12, 15, 16 demonstrating early anaerobic metabolism during exercise in patients with this disorder.

Determinants of the enhanced ventilatory response in the patient group. Individual regression equations for Ve vs VCO2 demonstrated excellent correlations in the patient group (all r > .92, p < .001). Very weak relationships were found between maximal exercise Ve/VCO2 and pulmonary capillary wedge pressure or pulmonary artery pressure (figure 5, A and B); these relationships did not reach statistical significance after adjustment for multiple comparisons. Maximal exercise cardiac output (figure 5, C) was inversely related to Ve/VCO2, although only a modest correlation was demonstrated. Peak exercise Ve/VCO2 was not related to arterial lactate (figure 5, D), but was closely correlated with Vd/Vt (figure 5, E). Ve/VCO2 was unrelated to Vt (figure 5, F) at peak exercise. Similar correlations were found with the above variables and Ve/VCO2 at rest and submaximal exercise. No relationships were seen between resting or exercise Ve/VCO2 and age, mixed venous blood gases, PaO2, pulmonary function abnormalities, or change in intrapulmonary vascular pressures during exercise. Resting and exercise Vd/Vt were related to cardiac output (all r < -.53, p < .01), but not to pulmonary intravascular pressures. Multivariate regression analysis showed that the addition of pulmonary vascular pressures to cardiac output did not enhance the correlation with Ve/VCO2 or Vd/Vt at rest or during exercise.

FIGURE 4. Resting and exercise hemodynamics and arterial lactate in patients with chronic heart failure (solid bars) and normal subjects (open bars). Bars represent mean ± SD. *p < .05 patients vs normal subjects; **p < .001 patients vs normal subjects.
To illustrate the effects of increased pulmonary capillary wedge pressures on exercise ventilation, patients were subdivided into groups with normal (<16 mm Hg) and abnormal (≥16 mm Hg) wedge pressures at peak exercise, as defined in this study and in previous investigations in our laboratory. There were no differences in Ve/CO₂, Vd/Vt, or VA/VO₂ in the 29 patients with normal wedge pressures vs the 35 patients with elevated pressures (table 2).

**Relationship of symptoms to ventilatory abnormalities.** Patients were asked in an unbiased fashion by personnel blinded to hemodynamic and ventilatory results whether dyspnea or fatigue was the main limiting symptom for each maximal exercise test. Almost all patients reported some dyspnea and some fatigue during each exercise bout. Sixty patients reported the same symptom on each of two (n = 40) or three occasions (n = 20). Only four patients did not report the same limiting symptom on repeat exercise testing or were equally limited by both symptoms, demonstrating good day-to-day reproducibility of this symptom reporting technique. Sixteen patients were limited primarily by dyspnea and 44 patients by fatigue. Data from the four patients with varying limiting symptoms were excluded from the following analysis. There were no differences in peak exercise hemodynamics, lactate, VO₂, Ve/CO₂, ventilation, or Vt in these two groups (table 3). The FEV₁ was lower in the group complaining of dyspnea (2.22 ± 0.50 liters) than in the group complaining of fatigue (2.77 ± 0.61 liters) (p = .02). The dyspnea index, Vt, or peak ventilation to maximal voluntary ventilation ratio, tended to be higher in the dyspnea group (0.64 ± 0.13) than in patients complaining of fatigue (0.55 ± 0.15), but this difference did not reach statistical significance (p = .16). Similarly, the ratio of peak Vt to FEV₁ was 0.69 ± 0.13 in the patients complaining of dyspnea and 0.61 ± 0.13 in those with fatigue (p = .16).

**Discussion**

In normal subjects exercise ventilation is determined by three factors according to the modified alveolar gas formula: (1) the PaCO₂ "set point" or the level at which PaCO₂ is regulated, (2) the Vd/Vt ratio, and (3) metabolic CO₂ production or VCO₂. Experimental manipulation of these three variables in man and in animals has not demonstrated an uncoupling of these relationships. In normal subjects ventilatory control links ventilation with VCO₂ to maintain PaCO₂ within a narrow range during moderate exercise. Our study and that of Fink et al. have demonstrated that this relationship is also present in patients with chronic heart failure. However, the Ve/CO₂ relation-

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**TABLE 2**

**Comparison of pulmonary, hemodynamic, and ventilatory variables at peak exercise in patients with normal (<16 mm Hg) (n = 29) and elevated (≥16 mm Hg) (n = 35) peak exercise PCWPm**

<table>
<thead>
<tr>
<th>Peak exercise variable</th>
<th>Normal PCWPm (9.7 ± 3.9 mm Hg)</th>
<th>Elevated PCWPm (29.4 ± 9.3 mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ve/CO₂</td>
<td>36.8 ± 7.4</td>
<td>38.3 ± 9.9</td>
</tr>
<tr>
<td>Vd/Vt</td>
<td>0.37 ± 0.06</td>
<td>0.35 ± 0.14</td>
</tr>
<tr>
<td>VA/VO₂</td>
<td>24.8 ± 1.9</td>
<td>26.3 ± 4.6</td>
</tr>
</tbody>
</table>

PCWPm = mean pulmonary capillary wedge pressure.

*No intergroup comparison was p < .05 by unpaired Student’s t tests.*

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**TABLE 3**

**Comparison of pulmonary, hemodynamic, and ventilatory variables in patients with chronic congestive heart failure grouped by the major symptom limiting exercise**

<table>
<thead>
<tr>
<th>Peak exercise variable</th>
<th>16 patients limited by dyspnea</th>
<th>44 patients limited by fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO₂ (ml/min)</td>
<td>1175 ± 289</td>
<td>1148 ± 323</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>22.1 ± 13.3</td>
<td>19.8 ± 12.2</td>
</tr>
<tr>
<td>PAPm (mm Hg)</td>
<td>39.3 ± 16.4</td>
<td>37.7 ± 17.3</td>
</tr>
<tr>
<td>Lactate (mM/l)</td>
<td>5.5 ± 1.8</td>
<td>5.1 ± 1.9</td>
</tr>
<tr>
<td>Ve/CO₂</td>
<td>38.1 ± 11.7</td>
<td>37.6 ± 8.0</td>
</tr>
<tr>
<td>Ve (l/min)</td>
<td>52.7 ± 15.3</td>
<td>52.7 ± 14.4</td>
</tr>
<tr>
<td>Vd/Vt</td>
<td>0.39 ± 0.33</td>
<td>0.36 ± 0.10 *</td>
</tr>
</tbody>
</table>

PCWP = pulmonary capillary wedge pressure; PAPm = mean pulmonary artery pressure.

*No intergroup comparison was p < .05 by unpaired Student’s t tests.*
ship is shifted upward at rest and during exercise in the presence of this disorder. Two mechanisms may be responsible for this: (1) an elevated Vd/Vt ratio, or (2) a decreased PacO₂ regulatory set point, which may be due to abnormal reflex mechanisms.

The finding that arterial PacO₂ and VA/VCO₂ were maintained at normal levels in our patients with chronic heart failure suggests that neural and chemoreceptor-mediated ventilatory control mechanisms are intact and function normally despite abnormal hemodynamic and metabolic exercise responses. The normal PacO₂ control and the demonstration of a strong relationship between Ve/VCO₂ and Vd/Vt indicates that heightened ventilation represents an appropriate response to increased pulmonary dead space in patients with chronic heart failure. Our data do not support the concept that hemodynamic abnormalities, including elevated pulmonary wedge pressures, act to stimulate reflex mechanisms that directly increase ventilation at rest or during exercise.

These findings provide a physiologic basis for prior observations of the existence of a ventilatory anaerobic threshold in the presence of chronic heart failure that depends on a close coupling of Ve with VCO₂. Although the Ve/VCO₂ and Ve/VO₂ curves are shifted upward during a graded maximal exercise protocol in heart failure, the curves maintain a normal configuration in most patients. This represents a normal response to metabolic stimuli during exercise that is superimposed on ventilatory adjustments to increased pulmonary dead space.

Rubin and Brown also observed elevated Vd/Vt ratios and ventilation during exercise in patients with chronic heart failure. The present study extends these findings by analyzing ventilatory control in chronic heart failure by assessing the components of the alveolar gas equation. The results of our study do not agree with those of Gazetopoulos et al., who concluded that increased pulmonary capillary wedge pressures caused “excess” exercise ventilation in heart failure. However, Gazetopoulos et al. also found a relationship between decreased cardiac output and increased ventilation in their patients. This observation may reflect the inverse relationship of cardiac output and pulmonary wedge pressure that has been described in patients with valvular heart disease. Because many of our patients had normal pulmonary wedge pressures despite decreased cardiac outputs, it was possible to analyze the separate effects of each variable on ventilation. Our finding that pulmonary wedge pressure was unrelated to ventilatory abnormalities indicates that intrapulmonary vascular pressures were not an important factor in determining ventilation in our patient group. This finding is supported by Fink et al., who also found no relationship between exercise Ve/VCO₂ and pulmonary wedge pressures and no change in exercise ventilation in patients with chronic heart failure after acute reduction in pulmonary wedge pressures with drug administration. However, our results do not exclude the possibility that chronically elevated pulmonary capillary wedge pressures may lead to pulmonary vascular or parenchymal abnormalities that may increase pulmonary dead space and therefore exercise ventilation in this disorder.

It has been suggested that the decreased Vt response to exercise may be important in causing an elevated Vd/Vt ratio and exercise hyperpnea in patients with heart failure. Decreased Vt did contribute to increased Vd/Vt at rest in our patients. Although our data indicated that Vt for a given ventilatory volume was reduced in patients, the increase in this variable at each workload was entirely normal. Therefore, when intergroup Vd/Vt comparisons were made at matched workloads, decreased Vt did not contribute to abnormalities in the patient group. The restrictive pulmonary function abnormalities seen in our patients are similar to those previously reported in patients with heart failure without concomitant pulmonary disease, and may have acted to attenuate the Vt response to exercise.

Although Vt for a given ventilatory volume was reduced, the primary mechanism causing exercise hyperpnea in our patient with chronic heart failure was the abnormal increase in dead space per breath. Since anatomic dead space should not be different in the groups at rest and would change in a similar fashion during exercise, the increase was likely due to an elevation in physiologic dead space. Two factors have been identified in chronic heart failure that may contribute to increased physiologic dead space: (1) pulmonary parenchymal abnormalities, and (2) dynamic ventilation perfusion mismatching. Although the present study does not clearly separate the relative contribution of these two factors, the inverse relationship of cardiac output with Ve/VCO₂ and Vd/Vt suggests that decreased pulmonary perfusion may lead to increased physiologic dead space by heightening ventilation perfusion mismatching. Abnormalities in pulmonary blood flow in animal preparations may lead to marked elevation of the Vd/Vt ratio through this mechanism.

The hemodynamic data reported for our normal subjects agrees closely with those from previous studies of normal middle-aged men. The ventilatory
exercise data for the control group are comparable to those obtained in a study of 400 middle-aged subjects by Hensen et al.17 Previous studies18 have identified age-related increases in exercise Ve/VCO₂ in normal subjects that were also present in our control subjects. Age-matched normal standards are therefore essential when studying ventilation in individuals with this disorder.

It is difficult to determine the exact impact of increased Ve/VCO₂ on exertional dyspnea, a subjective symptom, in the presence of chronic heart failure. Our results do not indicate that increased Ve/VCO₂ is the primary factor causing dyspnea in this disorder. However, the FEV₁ was reduced and the dyspnea index⁶ tended to be elevated in those patients whose exercise was limited by breathlessness. As has been suggested by Weber and Szidon,19 it is likely that reduced lung compliance or respiratory muscle function is important in the pathophysiology of this symptom. It is possible that elevated Ve/VCO₂ acted as an added stress to the respiratory muscles, which when superimposed on intrinsic pulmonary disease, increased the work of breathing and may have caused dyspnea in those patients with the more severe pulmonary function abnormalities. This is supported by recent studies indicating that respiratory muscle proprioceptive impulses are important in the perception of dyspnea.40 Although this analysis uses subjective data and does not clearly define the genesis of dyspnea, it confirms previous observations that elevated pulmonary wedge pressure,9, 10, 16, 17, 39 does not provide a simple explanation for this symptom in chronic heart failure.

In conclusion, increased ventilation at rest and during exercise is present in patients with chronic heart failure that is not explained by early anaerobic metabolism. Increased ventilation is due to elevations in the Vd/Vt ratio and is unrelated to lactate production or increased pulmonary vascular pressures. Physiologic pulmonary dead space increases markedly during exercise in patients with chronic heart failure and is responsible for the increased Vd/Vt. The finding in our study that cardiac output was inversely related to Vd/Vt and Ve/VCO₂ raises the possibility that reduced lung perfusion during exercise may accentuate ventilation perfusion mismatching and increase pulmonary dead space. This mechanism may serve to link ventilatory abnormalities to the attenuated cardiac output response to exercise in patients with chronic heart failure. Neurohumoral ventilatory control appears to be intact and couples Ve with VCO₂ to maintain arterial Pco₂ homeostasis. Thus, activation of ventilatory reflex mechanisms due to hemodynamic or metabolic abnormalities is not an important cause of heightened exercise ventilation in ambulatory patients with stable chronic heart failure.

We gratefully acknowledge the technical assistance of Diane House, R.N., James P. Shaw, N.M.T., Donna Bowen, R.N., Jim Stanfield, N.M.T., and Debbie Repass, N.M.T., and the secretarial assistance of Ms. Yvonne Vann.

References
respiratory system. Bethesda, 1986, American Physiologic Society, p 595

Erratum

Four equations in appendix 3 of the above article were reproduced incorrectly. The accurate equations are as follows:

Equation 9A \[ SW = E_a\left\{E_{es}/(E_a + E_{es})\right\}^2\{V_{ed} - V_{o}\}^2 \]

Equation 27A \[ dE/dt = E_{es} \cdot 2\theta \sin(\theta) \cos(\theta) = E_{es} \cdot \theta \cdot \sin(2\theta) \]

Equation 30A \[ E_{es} (V_{ed} - V_{o}) - 2\theta^2 \cos(2\theta) = 0 \]

Equation 37A \[ \sin^2(\theta) = E_a/(E_a + E_{es}) \]
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