Respiratory and Circulatory Analysis of CO₂ Output During Exercise in Chronic Heart Failure

Rory Hachamovitch, MD; Harvey V. Brown, MD; and Stanley A. Rubin, MD

Background. The output of carbon dioxide (VCO₂) is controlled by both hemodynamics and ventilation. To understand VCO₂ in patients who have chronic heart failure (CHF), we studied 14 patients who had New York Heart Association functional class III failure by measurements of hemodynamics, ventilation, and arterial and venous blood gases at rest and at 50 W of cycle ergometry exercise.

Methods and Results. Fick principle analysis of VCO₂ showed that because of a limited increase in cardiac output, CHF patients widened their venoarterial CO₂ content difference from 4.9±3.5 ml/dl at rest to 11.1±4.0 ml/dl with exercise (p<0.05). This increase in CO₂ content difference was achieved with no change in venous CO₂ content (from 54.3±3.3 ml/dl at rest to 54.5±4.8 ml/dl at exercise, p=NS); however, there was a decrease of arterial CO₂ content (from 49.4±3.7 ml/dl at rest to 43.4±2.3 ml/dl with exercise, p<0.05). Modeling of the CO₂ tension–content relation showed that there would have been a small, nonproportional increase of venous CO₂ content as venous CO₂ tension increased from 43.2±1.8 mm Hg at rest to 55.3±4.2 mm Hg during exercise (p<0.05); however, the development of metabolic acidosis during exercise entirely blunted the increase of CO₂ content. In contrast, both the shape of the tension–content relation and the acidosis of exercise further influenced the decrease of arterial CO₂ content as arterial CO₂ tension decreased from 37.0±2.9 mm Hg at rest to 32.0±3.4 mm Hg during exercise (p<0.05) as a result of excess ventilation.

Conclusions. In CHF patients during exercise, the circulatory limitations imposed by a low cardiac output on VCO₂ are compensated by a widened venoarterial CO₂ content difference. The content difference is not widened through an increase of venous CO₂ content but rather by a decrease of arterial CO₂ content caused by arterial hypocapnia and metabolic acidosis. (Circulation 1991;84:605–612)

The principles of both the hemodynamic and respiratory mechanisms of gas transport have been well described. In patients who have chronic heart failure (CHF), the mechanisms of O₂ uptake and transport have been thoroughly investigated during exercise, whereas little has been reported about the analysis of CO₂ output (VCO₂) and transport. This discrepancy between the two respiratory gases does not represent an indifference to the importance of VCO₂; it demonstrates the difficulty in obtaining the necessary data to understand the relations between blood gases and the hemodynamic and respiratory aspects of VCO₂. In this study, we were able to obtain complete data and to analyze blood CO₂ content. We hypothesized that unusual aspects of blood gases and CO₂ content would be resolved by analysis of the blood CO₂ tension–content relation in CHF patients during exercise. As an outcome of our investigation, we found that the CO₂ tension–content relation is substantially influenced by abnormal hemodynamics with its resultant metabolic acidosis and by excess ventilation with its resultant arterial hypocapnia.

Methods

Subjects

The study population comprised 26 men: 12 normal subjects and 14 CHF patients (Table 1). There were no differences in age, body weight, or body surface area between the groups. The CHF patients had known organic heart disease resulting from either chronic ischemic heart disease with prior myocardial infarction or idiopathic cardiomyopathy. They were all New York Heart Association (NYHA) functional class III. Although chronically symptomatic, none was
Instrumentation

All the methods used in this report have been previously described in detail.8–11 In brief, the electrocardiogram was recorded from the V_{5} (CM_{2}) position of the chest leads, and heart rate was manually counted from the tracing. A right heart flotation catheter (Swan-Ganz) was placed in the pulmonary artery. It was used to measure intracardiac pressures and cardiac output and to sample mixed venous blood. Cardiac output was measured by the thermodilution technique using a cardiac output computer. A catheter was placed in the radial artery and connected to an electronic manometer for measurement of systemic blood pressure and to sample arterial blood. Arterial and mixed venous (pulmonary artery) oxygen and carbon dioxide tensions and pH were measured on a blood gas analyzer (model 175, Dow Corning), and oxygen saturation and hemoglobin concentration were measured on a high-precision oximeter (model 282, Instrumentation Laboratories). Subjects respired through a low-resistance, low-dead-space valve (Hans Rudolph or Otis McKerrow), and expiratory gas volume was directed through a pneumotachygraph head (Hans Rudolph) connected to a differential pressure transducer (Validyne). Expired gas volumes were collected in meteorological balloons, and the fractional concentrations of expired gases were analyzed offline by a medical mass spectrometer (model MGA 1100, Perkin Elmer).

Exercise

Heart failure patients were included in this study only if they could exercise for at least 10 minutes of incremental exercise to a work load of 50 W. Incremental exercise was performed on a Monark weight-flywheel cycle ergometer beginning with unloaded pedaling and increasing by 25-W increments. Immediately before exercise, the CHF patients and the normal subjects were monitored for 5 minutes. The duration of the exercise stages was 3 minutes, except at 50 W, when duration was prolonged to 4 minutes to accommodate additional data collection. CHF patients were limited by fatigue and dyspnea at 50 W of exercise but had no symptoms of angina, whereas the normal subjects were not limited by this workload. All CHF patients and normal subjects were in normal sinus rhythm throughout the study, without serious or prolonged arrhythmias and with only rare premature ventricular contractions.

Data Collection and Analysis

Each variable was measured during the last minute at rest and at each stage of exercise (unloaded pedaling, 25 and 50 W). Heart rate and gas exchange were averaged over the entire 1-minute time period. Vascular pressures were averaged over a 15-second period. Blood gas samples were drawn over a 10–20-second period. Ventilation parameters were measured at each stage of exercise, whereas blood gas and hemodynamic data were collected at rest and at 50 W of exercise.

Calculations

Calculations for hemodynamic and ventilatory variables were performed as previously described.5,8,9 Plasma CO_{2} content (C_{p}) was calculated from the standard formula derived from the Henderson-Hasselbalch equation:

\[
C_{p} = 2.266 \cdot s \cdot PCO_{2} \cdot (1 + 10^{pH - pK'})
\]  

(1)

where \( s \) is a constant, \( PCO_{2} \) is CO_{2} tension, and \( pK' \) is the pH-adjusted negative log of the dissociation constant of carbonic acid. Blood CO_{2} content (C_{b}) was calculated from modern constants based on \( C_{p} \), hemoglobin concentration (Hb), and oxygen saturation (SO_{2})12:

\[
C_{b} = C_{p} \cdot \{1 - [0.289 \cdot Hb/(3.352 - 0.456 \cdot SO_{2})] \\
\cdot (8.142 - pH)]\}
\]  

(2)

CO_{2} flux was calculated as the product of \( C_{b} \) and cardiac output.

To obtain a better understanding of the relationship of P_{CO_{2}} and CO_{2} content, we modeled this relation over a range of physiological values of each. Because pH also influences this relation, we also included in the model the effects of acid-base balance.13 This results in a family of curves, each of which reflects the relation between P_{CO_{2}} and CO_{2} content at a particular value of base excess. This modeling permitted us to observe the relation of these three variables as they change codependently during exercise.
TABLE 2. Ventilation

<table>
<thead>
<tr>
<th></th>
<th>Ve (l/min)</th>
<th>VCO₂ (ml/min)</th>
<th>VO₂ (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal controls</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Rest</td>
<td>12.7±3.0</td>
<td>232±49</td>
<td>282±65</td>
</tr>
<tr>
<td>50 W</td>
<td>41.2±5.1</td>
<td>1,017±105</td>
<td>1,035±110</td>
</tr>
<tr>
<td>Chronic heart failure patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>14.6±3.5</td>
<td>256±71</td>
<td>290±64</td>
</tr>
<tr>
<td>50 W</td>
<td>45.3±10.2</td>
<td>903±219</td>
<td>776±173</td>
</tr>
</tbody>
</table>

*p*

Normal controls vs. chronic heart failure patients

Rest vs. exercise: NS NS NS

Group vs. exercise: NS NS <0.05

Ve, minute ventilation; VCO₂, carbon dioxide production/output; VO₂, oxygen consumption.

Statistical Analysis

A two-factor, repeated-measures analysis of variance was used to test for differences in the variables. Three null hypotheses were tested: that there was no effect of the patient group on the variable under observation (indicated as “normal controls versus CHF patients” in the tables); that there was no effect of the level of exercise on the variable under observation (indicated as “rest versus exercise” in the tables); and that there was no interaction between exercise and patient group (“special” or confounding effect on the CHF group by exercise, which is indicated as “group versus exercise” in the tables). After tests for overall effect, the paired t test was used to isolate differences between rest and exercise for individual groups, whereas the unpaired t test was used to isolate differences between normal subjects and CHF patients. Simple regression analysis was used to obtain correlation coefficients. A computer-based statistical package was used for these analyses (BMDP P2V and P1R).

Group data values are reported as mean±SD. A probability value of 0.05 was considered significant.

Results

Ventilation

Minute ventilation (Ve), oxygen uptake (VO₂), and carbon dioxide output (VCO₂) significantly increased in both normal subjects and CHF patients during exercise (Table 2). At 50 W of exercise, VO₂ was significantly lower in the CHF group at 776±173 ml/min compared with the measured value in normal subjects of 1,035±110 ml/min (p<0.05). It is possible that maximal VO₂ was exceeded in the CHF group, which caused anaerobic metabolism. This was supported by the respiratory exchange ratio at 50 W, which was substantially elevated above 1.0 in the CHF group and significantly greater than in the normal group (1.15±0.15 versus 0.99±0.09, p<0.01). Ventilatory equivalent for VCO₂ (Ve/VCO₂) at rest was 55.5±9.8 in the normal group and 57.4±10.9 in the CHF group. There was a significant decrease of Ve/VCO₂ in the normal group at 50 W of exercise to 41.4±3.5 (p<0.01) but only a small and nonsignificant decrease in the CHF group to 53.3±14.1 (p=NS). This significantly greater Ve/VCO₂ in the CHF group during exercise reflected both greater ventilation and lesser VCO₂.

Hemodynamics

Hemodynamic abnormalities in the CHF group were found to be consistent with those expected in this disease at rest and were magnified during exercise (Table 3). No abnormalities were noted in the normal group. At 50 W of exercise, cardiac output was 9.3±1.3 l/min at the normal group and 6.5±1.3 l/min in the CHF group, a between-group difference of 43% (p<0.01). At 50 W of exercise, a statistically significant inverse correlation was found between Ve/VCO₂ and cardiac output both in the normal group (r=-0.71, p<0.02) and the CHF group (r=-0.79, p<0.001), whereas no significant correla-

TABLE 3. Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>HR (beats/min)</th>
<th>MAP (mm Hg)</th>
<th>CO (l/min)</th>
<th>MPA (mm Hg)</th>
<th>PCW (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>75±10</td>
<td>99±13</td>
<td>4.7±1.0</td>
<td>11±3</td>
<td>3±3</td>
</tr>
<tr>
<td>50 W</td>
<td>112±20</td>
<td>127±28</td>
<td>9.3±1.3</td>
<td>21±5</td>
<td>8±3</td>
</tr>
<tr>
<td>Chronic heart failure patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>89±17</td>
<td>87±14</td>
<td>4.2±1.2</td>
<td>32±14</td>
<td>20±12</td>
</tr>
<tr>
<td>50 W</td>
<td>113±14</td>
<td>95±18</td>
<td>6.5±1.3</td>
<td>47±10</td>
<td>30±9</td>
</tr>
</tbody>
</table>

*p*

Normal controls vs. chronic heart failure patients

Rest vs. exercise: <0.05 <0.05 <0.05 <0.05 <0.05

Group vs. exercise: <0.05 <0.05 <0.05 NS NS

HR, heart rate; MAP, mean arterial pressure; CO, cardiac output; MPA, mean arterial pressure; PCW, pulmonary capillary wedge pressure.
During exercise, Gases the group. At with the normal group and hypoxic group (32.0±3.4 mm Hg, r=0.22; CHF group, r=0.37).

**Blood Gases**

Arterial carbon dioxide tension (Paco2, Table 4) at rest was 36.1±1.6 mm Hg in the normal group and 37.0±2.9 mm Hg in the CHF group. During exercise, there was a significant decrease of Paco2 in the CHF group (32.0±3.4 mm Hg, p<0.01), whereas no change occurred in the normal group (37.2±2.3 mm Hg, p=NS). This marked hypocapnia of the CHF group during exercise was notable when contrasted with the relative eucapnia of the normal group. In the CHF group, there was a significant inverse correlation between Paco2 and Ve/VCO2 (r=0.59, p<0.05), whereas the correlation was not significant in the normal group (r=0.42, p=NS). Arterial oxygen tension (Pao2, Table 4) at rest was 84.7±9.3 mm Hg in the normal group and 85.1±10.5 mm Hg in the CHF group. At 50 W of exercise, both groups maintained a normal Pao2 without a significant difference between the groups, and no patient in either group was found to be hypoxic at rest or during exercise.

Arterial pH (Table 4) at rest was 7.44±0.04 in the normal group and 7.45±0.04 in the CHF group. During exercise, pH was unchanged in the CHF group because the hyperpnea-induced hypocapnia was balanced by the development of metabolic acidosis, as shown by a significant decrease of arterial bicarbonate (p<0.01, Table 4). In the normal group, pH was also unchanged but without the development of either metabolic acidosis or a change in Paco2.

Venous CO2 tension (PvCO2, Table 4) at rest was 41.7±1.3 mm Hg in the normal group and 43.2±1.8 mm Hg in the CHF group. There was a substantial increase in PvCO2 during exercise in both groups, but the increase was significantly greater in the CHF group than in the normal group (55.3±4.2 versus 49.6±2.5 mm Hg, respectively; p<0.05). This venous hypercapnia, especially in the CHF group, reflected an increased tissue CO2 production as well as a low level of tissue flow. Venous oxygen tension (Pvo2, Table 4) at rest was 32.5±1.8 mm Hg in the normal group and 30.3±3.7 mm Hg in the CHF group. There was a progressive decrease of Pvo2 during exercise in both groups. This was significantly greater in the CHF group than in the normal group, which reflected greater peripheral extraction and caused a wider arteriovenous oxygen content difference (13.8±1.8 ml/dl in the CHF group versus 11.1±1.2 ml/dl in the normal group, p<0.05).

Venous pH (Table 4) at rest was 7.41±0.03 in the normal group and 7.41±0.02 in the CHF group. Significant venous acidosis developed in both groups during exercise, but it was substantially greater in the CHF group. The cause of the acidosis included both tissue
In a subset of eight normal subjects and nine CHF patients, CO₂ content and flux were calculated and examined in light of the model shown in Figure 1. Arterial CO₂ content at rest was 45.8 ± 2.8 ml/dl in the normal group and 49.4 ± 3.7 ml/dl in the CHF group (Table 5). Arterial CO₂ content decreased significantly during exercise in the CHF group to 43.4 ± 2.3 ml/dl (p < 0.01), which reflected both a decrease of Pco₂ and the development of metabolic acidosis (Table 4 and Figure 1), whereas it remained virtually unchanged in the normal group because of minimal changes in both variables. Arterial CO₂ flux at rest was 2,070 ± 460 ml/min in the normal group and 2,270 ± 610 ml/min in the CHF group. With exercise, flux increased significantly in both groups but to a greater extent in the normal group because of their larger cardiac output and CO₂ content.

In this same subset, venous CO₂ content at rest was 50.8 ± 3.8 ml/dl in the normal group and 54.3 ± 3.3 ml/dl in the CHF group (Table 5). Venous CO₂ content was virtually unchanged with exercise in the CHF group, which reflected the opposing effects of increased Pco₂ and the development of metabolic acidosis (Table 4 and Figure 1), whereas it increased in the normal group because of the unopposed effects of an increased Pco₂. Venous CO₂ flux at rest was 2,300 ± 530 ml/min in the normal group and 2,480 ± 570 ml/min in the CHF group. At 50 W of exercise, flux increased significantly in both groups, but the increase was substantially greater in the normal group, which reflected greater cardiac output (venous return).

Venoarterial CO₂ content difference increased from rest to exercise in both groups, but at 50 W it was significantly greater in the CHF group (11.1 ± 4.0 ml/dl) than in the normal group (7.0 ± 2.3 ml/dl, p < 0.05). The means by which the venoarterial CO₂ content difference increased from rest to exercise was different in the two groups. In the CHF group, the venoarterial content difference widened from rest to exercise because arterial CO₂ content decreased, whereas venous CO₂ content did not change. In the normal group, the content difference widened from rest to exercise, largely because of an increase in venous CO₂ content.

Discussion

Many investigations of gas transport during exercise in CHF patients have measured the hemodynamics and respiration of O₂ uptake and transport.4,6,11,12,15,17 However, few have studied the other major respiratory gas exchange—CO₂ output (VCO₂) and transport.3,7 VCO₂ is linked to both the circulation through the Fick equation and respiration through the level of ventilation. In the present study, we sought to examine both hemodynamics and ventilation to understand their relation in CO₂ gas transport. From the Fick equation, we found that CHF patients during exercise had reduced cardiac output that caused an increase of the venoarterial CO₂ content difference to maintain VCO₂. Our data showed that CO₂ content difference

![Graph](image_url)

**Figure 1.** Plot of blood Pco₂ vs. CO₂ content. Model is predicted from equations as described in “Methods.” There is a curvilinear relation so that curve is flattened with respect to Pco₂ axis. For physiological purposes, relation can be modeled as a family of curves of base excess: Metabolic acidosis causes a downward shift of curve and therefore a lower CO₂ content at any Pco₂. Actual data from patients with chronic heart failure are plotted on curves. Left: Arterial values. Right: Venous values. Solid lines: Pco₂ vs. CO₂ content relation at rest value of base excess (2.4 meq/l). Dashed lines: Relation at value of base excess at 50 W of exercise (~0.5 meq/l). Arterial CO₂ tension and content decrease from point A₁ at rest to point A₂ with exercise. In absence of development of metabolic acidosis, CO₂ content would decline only to point A₃. Vertical distance between points A₁ and A₂ represents arterial contribution to venoarterial CO₂ content difference developed during exercise. Venous CO₂ tension and content change from point V₁ at rest to point V₂ with exercise. In absence of a metabolic acidosis, CO₂ content would increase to point V₃. Vertical distance between points V₁ and V₂ represents minimal venous contribution to venoarterial CO₂ difference. Point V₃ represents venous CO₂ content and tension values that would permit entire venoarterial CO₂ content difference to be generated by venous side with no change in arterial CO₂ content. Note that both venous curves are slightly higher than their arterial counterparts; this is because of the lowered oxygen saturation of venous side, which by the Christiansen-Douglas-Haldane effect alters whole-blood CO₂ content.

Respiratory and metabolic components in the CHF group but only tissue respiration in the normal group.

**Modeling of CO₂ Content and Transport**

The modeled relation between Pco₂ and CO₂ content for whole blood is shown in Figure 1. The relation is nonproportional and curvilinear toward the tension axis. The shape of the curve shows that at arterial levels of Pco₂ found in the present study, the relative change of CO₂ content is enhanced when tension changes, whereas at venous levels of Pco₂ found in this study, the relative change of CO₂ content is blunted when tension changes. There is a family of content curves at different levels of acid-base balance, so decreases of base (metabolic acidosis) cause a decrease of CO₂ content at any level of Pco₂.
was widened through a decrease of arterial CO₂ content, whereas venous CO₂ content remained unchanged. From the level of ventilation, we found that CHF patients during exercise developed excess ventilation—ventilation beyond that needed to maintain eucapnia—which resulted in arterial hypocapnia. These observations led us to analyze the blood CO₂ tension–content relation. Of the factors that affect CO₂ content and venoarterial content difference, the development during exercise of metabolic acidosis was the main limitation to venous content, whereas both acidosis and hypocapnia resulted in reduced arterial CO₂ content.

The circulatory transport of VCO₂ can be analyzed by application of the Fick principle:

\[ VCO_2 = \frac{CO \cdot (CV_b - CA_b)}{CV_b} \]

where CO is cardiac output and CV₉ and CA₈ are the CO₂ contents of venous and arterial blood, respectively. As reported in many studies, but nevertheless central to our analysis, cardiac output was markedly depressed during exercise in CHF patients compared with normal subjects.⁸,¹⁸ Thus, to achieve any particular level of VCO₂ in the steady state, the CHF patients are required to widen their venoarterial CO₂ content difference in comparison with normal subjects. This can be achieved by either an increased venous content or a decreased arterial content. Therefore, the determinants of blood CO₂ content are important.

Plasma and blood CO₂ content are a function of both PCO₂ and pH, as shown in Equations 1 and 2 in "Methods." This relation is further complicated by the inverse relation between PCO₂ and pH at any level of acid-base balance. When blood is tonometered, the resulting relation between PCO₂ and CO₂ content is nonproportional, so changes of CO₂ content in the venous blood (higher PCO₂) are achieved only by greater changes of PCO₂ than are changes in CO₂ content in the arterial blood (lower PCO₂).¹⁹ There is a family of curves for different levels of acid-base balance. With the development of metabolic acidosis, there is a downward shift in the curve that results in a lower CO₂ content for any level of PCO₂ (Figure 1).

Despite an inference that an increase of venous PCO₂ during exercise in CHF patients would be the main factor in widening the venoarterial CO₂ content difference, other parameters determined the actual outcome. In the venous blood, the substantial increase of PCO₂ was accompanied by the development of metabolic acidosis. The increase of venous PCO₂ represented an increase of tissue respiration, whereas the metabolic acidosis was attributable to tissue anaerobic conditions from the inadequate blood flow of cardiac failure. These two effects were opposed in their action on venous blood CO₂ content: The metabolic acidosis entirely blunted the effect of the increase of Pco₂ with the result that venous CO₂ content did not change. In the arterial blood, Pco₂ moderately decreased concomitant with the development of metabolic acidosis. The decrease of arterial PCO₂ represented the effects of excess ventilation, whereas the metabolic acidosis resulted from the aforementioned inadequate cardiac output. These two effects were additive in their action on arterial CO₂ content: the metabolic acidosis exaggerated the effect of the decrease of PCO₂ with the result that arterial CO₂ content decreased. Therefore, the widened venoarterial CO₂ content difference during exercise in CHF patients occurred through the novel mechanism of a decrease of arterial content.

We examined other published reports of blood gas data obtained from CHF patients during exercise to study CO₂ transport. In two previous studies with similar patient populations to ours, arterial PCO₂ was also found to decrease during exercise in CHF patients.¹⁵,¹⁸ However, those studies did not include venous blood gas data, therefore it was not possible to analyze both the circulatory and respiratory aspects of CO₂ handling and transport. One previous study with complete arterial and venous data reported that arterial PCO₂ was unchanged and that venous PCO₂ increased slightly during exercise in CHF patients.⁷ However, there appear to be differ-

### Table 5. Carbon Dioxide Transport

<table>
<thead>
<tr>
<th>Arterial CO₂</th>
<th>Venous CO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Content</strong></td>
<td><strong>Flux</strong></td>
</tr>
<tr>
<td>(ml/dl)</td>
<td>(ml/min)</td>
</tr>
<tr>
<td>Normal controls</td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>45.8±2.8</td>
</tr>
<tr>
<td>50 W</td>
<td>45.4±3.3</td>
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<tr>
<td>Chronic heart failure patients</td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>49.4±3.7</td>
</tr>
<tr>
<td>50 W</td>
<td>43.4±2.3</td>
</tr>
</tbody>
</table>

| p | Normal controls vs. chronic heart failure patients | NS | <0.05 | NS | NS |
|   | Rest vs. exercise | <0.05 | <0.05 | NS | <0.05 |
|   | Group vs. exercise | <0.05 | <0.05 | NS | <0.05 |
ences between their study population and ours. We studied a homogeneous group of NYHA class III CHF patients, whereas they studied a diverse group of patients who were primarily of NYHA class II or III CHF, with smaller numbers of NYHA class I or IV CHF patients. At a comparable level of peak exercise, our patients had more severe hemodynamic derangements, which included a lower mean cardiac output (6.5 l/min versus approximately 7.5 l/min). Their results may reflect CHF patients with less severe circulatory failure. More advanced CHF may result in the mix of metabolic acidosis and excess ventilation that determined CO₂ handling and transport in our patients.

An appreciation of the factors that influence the CO₂ tension–content relation, especially metabolic acidosis, suggests that the limitation of venous CO₂ content and the decrease of arterial CO₂ content that we observed are not unique to CHF patients during exercise. We reanalyzed the data from two previous but very different clinical studies that reported venous and arterial blood gases. In one of the studies, normal subjects were exercised to a high intensity to obtain a range of blood gas values.12 We found that some of the subjects developed a widened venoarterial CO₂ content difference during exercise in which venous PCO₂ increased without a change in CO₂ content, whereas arterial PCO₂ decreased and was accompanied by a decrease in CO₂ content. In the other report, patients in an intensive care unit were studied during cardiopulmonary resuscitation.20 We also found that venous PCO₂ increased without a change in CO₂ content, whereas arterial PCO₂ decreased and was accompanied by a decrease in CO₂ content. We suspect that these examples may be supplemented by others in which relatively or absolutely low cardiac output requires a widened venoarterial CO₂ content difference to sustain VCO₂, but increases of venous CO₂ content are limited by the factors that shape the CO₂ tension–content relation.

What are the technical limitations to this study? Methodologically, we calculated (rather than directly measured) blood CO₂ content from classic equations that use blood gas parameters and were recently updated and validated from a numerical analysis of parameters that determine CO₂ content.12 That study demonstrated a very significant correlation (with a small standard deviation) between measured and calculated blood CO₂ content over a wide range of values inclusive of those in our study. Therefore, we are confident that the calculated values in our study are reproducible. We also recognize that our analysis of CO₂ output, which uses the Fick principle, is only applicable under steady-state conditions. However, we made every effort to achieve steady-state conditions by collecting data during minute 3–4 of the 50-W exercise period and by using sampling techniques that reflect average rather than instantaneous values.

This study raises the question of the interaction between hemodynamics and ventilation in satisfying the CO₂ transport requirements in the CHF patient. The mechanisms that limit cardiac output and therefore require a widened venoarterial CO₂ content difference during the development of metabolic acidoesis are well described. However, it is not clear whether the increased content difference is entirely dependent on the development of metabolic acidoesis through its effect on the CO₂ tension–content relation. Further, our data do not address the mechanisms of respiratory control that were responsible for excess ventilation and the subsequent arterial hypoxemia. The mechanisms responsible for these phenomena merit further investigation.

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KEY WORDS • excess ventilation • blood gases • Fick principle • chronic heart failure • cardiac output
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