Patients with cardiac diseases, especially those with congestive heart failure, frequently experience exertional dyspnea (1–5). They show a heightened ventilatory response to exercise, with the magnitude of the increase in ventilation related to the severity of heart failure (6,7). An inadequate cardiac output in cardiac patients during exercise causes hypoperfusion of working muscles, leading to anaerobic metabolism even at a low exercise intensity, and subsequently to lactate accumulation, acidosis and tissue hypoxia (3,8–11). These factors may contribute to muscle fatigue and shortness of breath in cardiac patients (3,10–13). On the other hand, cardiac patients often develop pulmonary congestion, which may reduce lung compliance, stimulate J receptors and induce rapid and shallow ventilation (14–16). Decreased cardiac output and pulmonary congestion in cardiac patients may cause changes in the distribution of ventilation and perfusion in the lungs (ventilation-perfusion mismatch), leading to an increased ratio of physiologic dead space to tidal volume (7,17,18). Thus, the ventilatory equivalent for carbon dioxide (CO₂) output and the slope of minute ventilation plotted as a function of CO₂ output are abnormally high in these patients (4,5,19).

In normal subjects, end-tidal CO₂ pressure (PETCO₂) is slightly lower than the partial pressure of arterial CO₂ (PaCO₂) at rest, but becomes higher than PaCO₂ during exercise as the work load increases (20–22). In patients with obstructive or restrictive lung diseases and with silent pulmonary embolism, PETCO₂ is below normal at rest and during exercise (23–25). PETCO₂ is also decreased in animals and patients with a decreased cardiac output who undergo cardiopulmonary resuscitation (26–29). These findings suggest that PETCO₂ is decreased in some pathophysiologic conditions associated with a ventilation-perfusion mismatch and a decreased cardiac output. Although there have been many studies reporting abnormalities in ventilatory parameters in cardiac patients, (3,8,9) only one report has shown that PETCO₂ at peak exercise is positively correlated with peak O₂ uptake in patients with chronic heart failure (7). Therefore, it has not been fully understood whether PETCO₂ is abnormal at rest and during exercise in cardiac patients. Moreover, if so, it is also unknown what mechanism(s) might be responsible for the decreased PETCO₂ in cardiac patients.

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We measured PETCO₂ in cardiac patients and normal subjects to determine whether PETCO₂ is abnormal in these patients. PETCO₂ is determined by the venous PCO₂, the degree of the ventilation-perfusion mismatch, and pulmonary blood flow (cardiac output) (30). Therefore, we also investigated the relationships of PETCO₂ with exercise capacity, cardiac output and ventilatory parameters, including CO₂ output, minute ventilation and the slope of the minute ventilation-CO₂ output relationships to clarify the mechanism(s) of decreased PETCO₂. We measured ventilatory parameters by breath-by-breath gas analysis, with simultaneous measurement of cardiac output by the dye dilution method.

METHODS

Subjects

We investigated 112 patients with cardiac diseases and 29 age-matched normal control subjects. Patients consisted of 67 men and 45 women with an average age of 53 ± 1 (SE) years. The underlying heart diseases included valvular heart diseases in 79 patients, old myocardial infarction in 24 patients, and idiopathic dilated cardiomyopathy in 9 patients. According to the New York Heart Association (NYHA) functional classification, 31 patients were in class I, 35 in class II, and 46 in class III. According to Weber and Janicki’s functional classification (3), 20 patients were in class A (peak O₂ uptake [VO₂] > 20 ml/min/kg), 36 in class B (peak VO₂ 16–20 ml/min/kg), 52 in class C (peak VO₂ 10–15 ml/min/kg), and 4 in class D (peak VO₂ < 10 ml/min/kg). Normal control subjects consisted of 20 men and 9 women, whose average age was 51 ± 3 years. They had no symptoms, and no evidence of significant disease was detected by physical examination, chest radiography, resting and exercise electrocardiograms (ECGs), or routine laboratory tests.

Excluded from the study were patients with aortic stenosis, unstable angina, congenital heart diseases with shunt, heart failure in NYHA class IV, metabolic diseases or primary lung diseases. No patient had a myocardial infarction within one month of study enrollment. All patients were clinically stable at the time of the study. Medications were discontinued as follows: beta-blockers were discontinued for at least seven days before initiation of the study, and other medications such as digitalis, diuretics and vasodilators were discontinued 24 h before the study. The study was approved by the hospital ethics committee and informed consent was obtained from all subjects.

Exercise Protocol and Expired Gas Analysis

Before the study, patients were asked to perform a familiarization exercise test with expired gas analysis, and then a symptom-limited exercise test on an electromagnetically braked upright cycle ergometer (Corival with ramp slope controller, Lode, Groningen, Holland) at least 2 h after a meal. The exercise protocol and gas exchange analysis have been previously described (31,32). In brief, after a 4-min rest on the cycle ergometer, exercise was started at 20 W for a 4-min warmup and was then increased in 1-W increments every 6 s. Patients were monitored by a 12-lead electrocardiogram using a stress system (ML-5000, Fukuda Denshi, Tokyo, Japan). Blood pressure was measured by an automatic indirect cuff manometer (STBP-780, Colin, Aichi, Japan) every minute. Patients stopped exercising because of leg fatigue or dyspnea. Expired gases were measured continuously in all patients on a breath-by-breath basis using an expired gas analyzer (RM-300, Minato Ikaagaku, Osaka, Japan). Ventilatory parameters, including oxygen (O₂) uptake, CO₂ output and minute ventilation, were calculated. Patients sometimes hyperventilated in anticipation of the tests and this tended to initially decrease PETCO₂. When the patients hyperventilated, resting time was extended beyond 4 min until a stable PETCO₂ was obtained.

Cardiac Output Measurement and Blood Gas Analysis

During cardiopulmonary exercise testing, cardiac output was measured in all subjects by the dye dilution method using an earpiece with a dye densitometer (MCL-4200, Nihon Coden, Tokyo, Japan) (33). A small cannula was placed in the antecubital vein, and 5 mg of indocyanine green was injected through this cannula at rest, at peak exercise, and every 2 min during exercise.

Arterial blood gases were measured in 53 cardiac patients and 15 normal control subjects. The underlying heart diseases included valvular heart diseases in 30 patients, old myocardial infarction in 18 patients and idiopathic dilated cardiomyopathy in 5 patients. Another small cannula was inserted in the brachial artery, and blood samples were obtained every minute throughout the test. The partial pressure of arterial O₂ (PaO₂) and PaCO₂ and the pH were measured with a standard blood gas analyzer (288 Blood Gas System, Chiba Corning Co., Medfield, Massachusetts).

Derived Parameters

The minute ventilation-CO₂ output curve obtained during exercise can be closely fitted as a linear line (6,19). The slope of the minute ventilation-CO₂ output relation from the start of ramp exercise to the respiratory compensation point

### Abbreviations and Acronyms

- **PETCO₂** = end-tidal CO₂ pressure
- **PaCO₂** = partial pressure of arterial CO₂
- **P(a-ET)CO₂** = arterial–end-tidal CO₂ difference
- **NYHA** = New York Heart Association
- **VO₂** = O₂ uptake
- **VD/VT** = the physiologic dead space to tidal volume ratio
- **%FVC** = forced vital capacity expressed as percent of predicted
- **%FEV₁** = forced expiratory volume in 1 s expressed as percent of predicted
- **VA/Q** = ventilation/perfusion
was calculated by linear regression analysis using the values of minute ventilation and CO₂ output.

The physiologic dead space to tidal volume ratio (VD/VT) was calculated using the equation (34):

$$\frac{VD}{VT} = \frac{(PaCO_2 - PeCO_2)}{PaCO_2 - VDM/VT},$$

where VT is tidal volume, PeCO₂ is mixed expired PCO₂ and VDM is breathing valve dead space.

**Statistics**

Comparisons of data among the four groups were performed using one-way analysis of variance (ANOVA) followed by Dunnett’s multiple comparison test. The effects of exercise on PETCO₂ and PaCO₂ variables were compared by two-way ANOVA with repeated measures. Differences between the means at each time point within and between groups were performed by one-way ANOVA followed by Dunnett’s multiple comparison test. The correlation coefficients were determined using the least-squares method. A value of p < 0.05 was considered significant. All data are shown as the mean ± SE.

**RESULTS**

The anaerobic threshold, oxygen uptake and work rate at peak exercise were lower in the patients than in the control subjects (Table 1). These parameters decreased with increases in the NYHA class. The slope of minute ventilation-CO₂ output relationship was higher in the patients than in the control subjects, and became higher with increases in the NYHA class.

PETCO₂ was lower in cardiac patients at rest than in normal subjects and decreased with increases in the NYHA class (control, 35.5 ± 0.4; NYHA I, 34.4 ± 0.6; II, 32.7 ± 0.7; III, 32.2 ± 0.5 mm Hg; p = 0.003, Fig. 1). PETCO₂ increased during exercise in patients and control subjects. There was a significant difference in the change of PETCO₂ during exercise among the four groups at each time point (one way-ANOVA at each time point: rest p = 0.0016, 20 W p = 0.0001, 30 W p = 0.0001, AT p = 0.0001, RC p = 0.0001, Peak p = 0.0001). PETCO₂ was significantly lower in the cardiac patients than in the normal subjects, and the difference became more marked as the exercise work rate increased.

PETCO₂ was lower in the cardiac patients than in the normal subjects at the same CO₂ output during exercise, and decreased with increases in the NYHA class (Fig. 2). PETCO₂ was lower in cardiac patients than in normal

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**Table 1. Results of Exercise Testing**

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>VE-V˙CO₂ slope</td>
<td>26.0 ± 1.3</td>
<td>26.5 ± 1.1</td>
<td>33.8 ± 1.6*†</td>
<td>38.5 ± 1.6*†‡</td>
</tr>
<tr>
<td>AT (ml/min/kg)</td>
<td>13.3 ± 0.6</td>
<td>13.5 ± 0.5</td>
<td>11.7 ± 0.3*†</td>
<td>9.7 ± 0.4*†‡</td>
</tr>
<tr>
<td>Peak VO₂ (ml/min/kg)</td>
<td>24.7 ± 0.9</td>
<td>21.1 ± 0.7*</td>
<td>15.7 ± 0.4*†</td>
<td>12.4 ± 0.3*†‡</td>
</tr>
<tr>
<td>Peak CI (l/min/m²)</td>
<td>9.41 ± 0.40</td>
<td>7.02 ± 0.32*</td>
<td>4.77 ± 0.21*†</td>
<td>3.83 ± 0.15*†‡</td>
</tr>
<tr>
<td>Peak work rate (W)</td>
<td>113 ± 7</td>
<td>97 ± 4*</td>
<td>79 ± 3*†</td>
<td>54 ± 4*†‡</td>
</tr>
</tbody>
</table>

NYHA indicates New York Heart Association functional classification; VE-V˙CO₂ slope, the slope of minute ventilation (VE)-CO₂ output (V˙CO₂) relationship; AT, anaerobic threshold; VO₂, oxygen uptake; CI, cardiac index.

Values are the mean ± SE, *p < 0.05 vs. controls, †p < 0.05 vs. NYHA I, ‡p < 0.05 vs. NYHA II.

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**Figure 1.** End-tidal CO₂ pressure (PETCO₂) at rest and during exercise according to the NYHA functional class. There was a significant difference in the change of PETCO₂ during exercise among the four groups at each time point (one way-ANOVA at each time point: rest p = 0.0016, 20 W p = 0.0001, 30 W p = 0.0001, AT p = 0.0001, RC p = 0.0001, Peak p = 0.0001). AT indicates anaerobic threshold; RC = respiratory compensation point; P = peak exercise. Values are mean ± SE. *p < 0.05 versus controls.
subjects during exercise when compared at the same values of minute ventilation, tidal volume and respiratory rate, and also became lower as the functional class worsened.

The relationship between PETCO₂ and cardiac index at rest and during exercise is also demonstrated in Figure 3. The relationship between PETCO₂ and cardiac index was linear. In cardiac patients, the cardiac index was smaller than in normal subjects at rest and during exercise, and as the cardiac index decreased the PETCO₂ also decreased. The decrease of PETCO₂ was more marked in patients with severe heart failure, as indicated by their NYHA functional class.

PETCO₂ at the respiratory compensation point correlated positively with the cardiac index at peak exercise \( (r = 0.582, p < 0.0001, \text{Fig. 4}) \). If less than 38.5 mm Hg (that is, mean–2 SD) of PETCO₂ at respiratory compensation point and a cardiac index of 5.11 l/min/m² at peak exercise were considered to be abnormal in the control subjects, abnormally low values of PETCO₂ were observed in 49 of the 64 patients who had decreased cardiac output. Thirty-six of the 48 patients who had normal cardiac output had a

\[
y = 1.349\times x + 31.9
\]

\[r = 0.582\]

\[p < 0.0001\]
Thus, the sensitivity and specificity of PETCO₂ for decreased cardiac output were 76.6% and 75.0%, respectively.

PETCO₂ at the respiratory compensation point correlated positively with O₂ uptake at peak exercise (r = 0.583, p < 0.0001, Fig. 5). Moreover, PETCO₂ at the respiratory compensation point was correlated with the slope of minute ventilation-CO₂ output relationship (r = -0.784, p < 0.0001).

In the subgroup of 53 patients and 15 normal subjects in whom arterial blood gases were measured, PaCO₂ was similar in both groups at rest and during exercise (Fig. 6). PETCO₂ was lower than PaCO₂ at rest in both patients and control subjects, but P(a-ET)CO₂ was greater in the patients than in the control subjects (9.54 ± 0.33 vs. 6.59 ± 0.55 mm Hg, p = 0.0001). There was a significant difference in the change between PaCO₂ and PETCO₂ variables and interaction with time both in the patients (variables p = 0.0001, interaction p = 0.0001, by ANOVA) and in the control subjects (variables p = 0.0001, interaction p = 0.0001, by ANOVA). At peak exercise, PETCO₂ increased above PaCO₂ in control subjects, but remained below PaCO₂ in patients. PETCO₂ at the respiratory compensation point was negatively correlated with the ratio of physiologic dead space to the tidal volume (r = -0.494, p < 0.0001, Fig. 7).

PaO₂ was similar in both the patient group and the normal control group, at rest and during exercise (at peak exercise; 93.0 ± 2.5 vs. 95.9 ± 1.9 mm Hg, p = 0.56). There were no intergroup differences in PAO₂ at rest or during exercise. P(A-a)O₂ was similar in both groups at rest and during exercise (at peak exercise; 18.9 ± 2.8 vs. 19.3 ± 1.7 mm Hg, p = 0.92).

Cardiac patients had lower values of forced vital capacity expressed as percent of predicted (%FVC) than did control subjects (control, 103 ± 3%; NYHA I, 94 ± 4%; II, 85 ± 3%; III, 79 ± 3%; p = 0.0001). Similarly, patients had lower values of forced expiratory volume in 1 s expressed as percent of predicted (%FEV₁) than did control subjects (control, 99 ± 3%; NYHA I, 88 ± 5%; II, 73 ± 3%; III, 72 ± 3%, p = 0.0001). However, patients had a similar FEV₁/FVC ratio to that in normal control subjects (control,

![Figure 6](image1.png)
PETCO₂ was lower at rest and during exercise in cardiac patients compared with normal subjects, and decreased in association with increases in the NYHA class. PETCO₂ was correlated with cardiac output during exercise, and the sensitivity and specificity of PETCO₂ regarding decreased cardiac output were good. PETCO₂ was also positively correlated with O₂ uptake and was negatively correlated with the slope of minute ventilation–CO₂ output relationship and the ratio of physiologic dead space to tidal volume. On the other hand, P(A-a)O₂ was similar in cardiac patients and in the normal control subjects at rest and during exercise. The present study demonstrates that PETCO₂ is abnormally regulated during exercise in patients with cardiac disease, and that the decrease in PETCO₂ is due to changes in the pulmonary circulation (pulmonary blood flow) and not in the airways.

Potential mechanisms

There was no intergroup difference in PaCO₂ between cardiac patients and normal subjects at rest and during exercise in the present study, which is consistent with previous findings (4). Although PaCO₂ was greater than PETCO₂ at rest in both the patients and the normal subjects, P(a-ET)CO₂ was greater in cardiac patients than in normal subjects at rest. During exercise, PETCO₂ increased in both patients and normal subjects in this study. In normal individuals, PETCO₂ increases because of the increased rate of CO₂ delivery to the lungs associated with the high rate of CO₂ production during exercise (30). During expiration, the alveolar CO₂ pressure (PaCO₂) approaches the venous PaCO₂ because fresh air does not dilute the alveolar gas. Because PETCO₂ is the highest PaCO₂ in the alveoli during the respiratory cycle and the arterial PaCO₂ represents the average alveolar PaCO₂, PETCO₂ is higher than PaCO₂ during exercise in normal individuals. However, in the present study, decreased PETCO₂ with positive P(a-ET)CO₂ was observed in cardiac patients during exercise. Although PETCO₂ is almost similar to PaCO₂ in perfused alveoli, it is lower than PaCO₂ in poorly perfused or high-ventilation/perfusion (VA/Q) alveoli (22,23,30). Therefore, the greater P(a-ET)CO₂ in cardiac patients suggests decreased perfusion to more ventilated alveoli (uneven alveolar VA/Q with high VA/Q units or increased alveolar dead space) in these patients.

The increase in cardiac output during exercise was inappropriately small relative to the work load in cardiac patients in the present study, which is consistent with previous reports (3,8–11). PETCO₂ is decreased in patients with a decreased cardiac output who undergo cardiopulmonary resuscitation (26,27,29), and changes in cardiac output in patients with pacemakers influence PETCO₂ at rest (35). Therefore, the inappropriate increase in cardiac output during exercise may have caused PETCO₂ to decrease in cardiac patients. Although Wasserman et al. (7), showed that PETCO₂ at peak exercise is positively correlated with peak O₂ uptake in patients with chronic heart failure, it has been unknown what mechanism(s), especially cardiac output, might be responsible for the decreased PETCO₂ in cardiac patients. On the other hand, this study clearly demonstrated that PETCO₂ increased in proportion to the cardiac index from rest to respiratory compensation point during exercise, and there were no intergroup differences in the slope of the PETCO₂–cardiac index relationship between normal subjects and cardiac patients (Fig. 3). PETCO₂ was correlated with cardiac index at peak exercise. These results suggest that the relatively low pulmonary blood flow is primarily responsible for the abnormally low levels in PETCO₂ during exercise, and that decreased perfusion of ventilated alveoli was a likely cause of the decreased PETCO₂.

Figure 7. Relationships of end-tidal CO₂ pressure (PETCO₂) at the respiratory compensation point with the ratio of physiologic dead space to tidal volume (VD/VT) in 53 cardiac patients and 15 normal control subjects.

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Because PETCO2 is also determined by the rate of CO2 production during exercise (30,34), a decrease in PETCO2 may reflect decreased CO2 production during exercise in cardiac patients. However, PETCO2 was lower in cardiac patients than in normal subjects at the same CO2 output, which was almost equal to CO2 production in the whole body. Therefore, the decrease in PETCO2 in these patients was not due to decreased CO2 production. PETCO2 was also lower in cardiac patients than in normal subjects at the same levels of minute ventilation, respiratory rate, and tidal volume, suggesting that the decrease in PETCO2 was not related to abnormal ventilation patterns (rapid and shallow breathing) or compensatory hyperventilation.

Minute ventilation is mainly determined by the rate of CO2 production, the physiologic dead space, and the level at which PaCO2 is regulated (20,22,36). Minute ventilation increases linearly with CO2 output to maintain a relatively stable arterial PaCO2 during exercise (20,22). In the present study, the slope of minute ventilation and CO2 output relationship was steeper in cardiac patients than in normal subjects and became more steep as the NYHA class became more severe. This is consistent with the findings of previous reports (6,19). This heightened ventilation was due to the ventilation-perfusion mismatch and the increase in dead space ventilation (7). Previous studies showed that heightened ventilation is due to failure of cardiac output to increase appropriately, but not to pulmonary congestion (4,19). In the present study, PETCO2 was negatively correlated with the slope of the minute ventilation-CO2 output relationship and with the ratio of physiologic dead space to the tidal volume. This study also showed that P(A-a)O2 was normal at rest and during exercise in cardiac patients, which was in agreement with the findings previously reported by Wasserman et al. (7). Taken together, these findings suggested that the high ventilation-perfusion mismatch occurs without a significant low ventilation-perfusion mismatch (perfusion is reduced or absent in the well-ventilated lung), and that the decrease in PETCO2 is due to changes in the pulmonary circulation and not in the airways. Therefore, the decreased PETCO2 in cardiac patients is considered to be derived from the ventilation-perfusion mismatch and the increased ratio of physiologic dead space to tidal volume, which were due mainly to the inappropriate increase in cardiac output during exercise.

Cardiac patients had lower values of %FVC and %FEV1 compared with normal control subjects, although their FEV1/FVC ratio was similar to that of normal control subjects. However, %FVC and %FEV1 were not markedly reduced in the majority of cardiac patients, partly because cardiac patients with underlying primary lung diseases were excluded from this study. PETCO2 correlated weakly with %FEV1, but not with %FVC or FEV1/FVC ratio. The reason might be the relatively narrow spread of values of %FEV1 in cardiac patients and normal control subjects observed in this study. Furthermore, PETCO2 was more influenced by the increase in cardiac output during exercise than by pulmonary function.

**Study Limitation**

Patients entered in this study were cardiac patients with or without chronic heart failure, but without lung diseases, such as chronic obstructive lung diseases or restrictive diseases. Therefore, the specificity as well as the sensitivity of PETCO2 as a means to evaluate cardiac output reserve are valid only for cardiac patients. Because PETCO2 may be abnormally low in patients with lung diseases who have a normal cardiac output (24), its sensitivity and specificity might be less if those patients were included with cardiac patients.

**CONCLUSIONS**

Patients with cardiac diseases had an abnormally low PETCO2 at rest and during exercise compared with normal subjects. PETCO2 was correlated with cardiac output during exercise, and the sensitivity and specificity of PETCO2 regarding decreased cardiac output were good. PETCO2 was also correlated with the slope of the relationship between minute ventilation and CO2 output, and the ratio of physiologic dead space to the tidal volume. PETCO2 may be a new marker of ventilatory abnormalities that reflects impaired cardiac output response to exercise in cardiac patients.

**REFERENCES**


