End-tidal CO_2 Pressure Decreases During Exercise in Cardiac Patients

Association With Severity of Heart Failure and Cardiac Output Reserve

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OBJECTIVES	We measured end-tidal CO_2 pressure ($PETCO_2$) during exercise and investigated the relationship between $PETCO_2$ and exercise capacity, ventilatory parameters and cardiac output to determine the mechanism(s) of changes in this parameter.
BACKGROUND	It is unclear whether $PETCO_2$ is abnormal at rest and during exercise in cardiac patients.
METHODS	Cardiac patients (n = 112) and normal individuals (n = 29) performed exercise tests with breath-by-breath gas analysis, and measurement of cardiac output and arterial blood gases.
RESULTS	$PETCO_2$ was lower in patients than in normal subjects at rest and decreased as the New York Heart Association class increased, whereas the partial pressure of arterial CO_2 did not differ among groups. Although $PETCO_2$ increased during exercise in patients, it remained lower than in normal subjects. $PETCO_2$ in relation to cardiac output was similar in patients and normal subjects. $PETCO_2$ at the respiratory compensation point was positively correlated with the O_2 uptake (r = 0.583, p < 0.0001) and the cardiac index at peak exercise (r = 0.582, p < 0.0001), and was negatively correlated with the ratio of physiological dead space to the tidal volume. The sensitivity and specificity of $PETCO_2$ to predict an inadequate cardiac output were 76.6% and 75%, respectively, when $PETCO_2$ at respiratory compensation point and a cardiac index at peak exercise that were less than the respective control mean−2 SD values were considered to be abnormal.
CONCLUSIONS	$PETCO_2$ was below normal in cardiac patients at rest and during exercise. $PETCO_2$ was correlated with exercise capacity and cardiac output during exercise, and the sensitivity and specificity of $PETCO_2$ regarding decreased cardiac output were good. $PETCO_2$ may be a new ventilatory abnormality marker that reflects impaired cardiac output response to exercise in cardiac patients diagnosed with heart failure. (J Am Coll Cardiol 2000;36:242–9) © 2000 by the American College of Cardiology

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 (CO_2) output and the slope of minute ventilation plotted as a function of CO_2 output are abnormally high in these patients (4,5,19).

In normal subjects, end-tidal CO_2 pressure ($PETCO_2$) is slightly lower than the partial pressure of arterial CO_2 ($PaCO_2$) at rest, but becomes higher than $PaCO_2$ during exercise as the work load increases (20−22). In patients with obstructive or restrictive lung diseases and with silent pulmonary embolism, $PETCO_2$ is below normal at rest and during exercise (23–25). $PETCO_2$ is also decreased in animals and patients with a decreased cardiac output who undergo cardiopulmonary resuscitation (26−29). These findings suggest that $PETCO_2$ 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 $PETCO_2$ at peak exercise is positively correlated with peak O_2 uptake in patients with chronic heart failure (7). Therefore, it has not been fully understood whether $PETCO_2$ 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 $PETCO_2$ in cardiac patients.

Abbreviations and Acronyms

PETCO₂	=	end-tidal CO_2 pressure
PaCO₂	=	partial pressure of arterial CO_2
P[a-ET]CO₂	=	arterial–end-tidal CO_2 difference
NYHA	=	New York Heart Association
V̇O₂	=	O_2 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

We measured $PETCO_2$ in cardiac patients and normal subjects to determine whether $PETCO_2$ is abnormal in these patients. $PETCO_2$ is determined by the venous PCO_2, the degree of the ventilation-perfusion mismatch, and pulmonary blood flow (cardiac output) (30). Therefore, we also investigated the relationships of $PETCO_2$ with exercise capacity, cardiac output and ventilatory parameters, including CO_2 output, minute ventilation and the slope of the minute ventilation-CO_2 output relationships to clarify the mechanism(s) of decreased $PETCO_2$. 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 O_2 uptake [$V̇O_2$] > 20 ml/min/kg), 36 in class B (peak $V̇O_2$ 16–20 ml/min/kg), 52 in class C (peak $V̇O_2$ 10–15 ml/min/kg), and 4 in class D (peak $V̇O_2$ < 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 Ikagaku, Osaka, Japan). Ventilatory parameters, including oxygen (O_2) uptake, CO_2 output and minute ventilation, were calculated. Patients sometimes hyperventilated in anticipation of the tests and this tended to initially decrease $PETCO_2$. When the patients hyperventilated, resting time was extended beyond 4 min until a stable $PETCO_2$ 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 O_2 (PaO_2) and PaCO_2 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-CO_2 output curve obtained during exercise can be closely fitted as a linear line (6,19). The slope of the minute ventilation-CO_2 output relation from the start of ramp exercise to the respiratory compensation point

Table 1. Results of Exercise Testing

	Controls	NYHA		
		I	II	III
V̇E-V̇CO$_2$ slope	26.0 ± 1.3	26.5 ± 1.1	33.8 ± 1.6*†	38.5 ± 1.6*†‡
AT (ml/min/kg)	13.3 ± 0.6	13.5 ± 0.5	11.7 ± 0.3*†	9.7 ± 0.4*†‡
Peak V̇O$_2$ (ml/min/kg)	24.7 ± 0.9	21.1 ± 0.7*	15.7 ± 0.4*†	12.4 ± 0.3*†‡
Peak CI (l/min/m^2)	9.41 ± 0.40	7.02 ± 0.32*	4.77 ± 0.21*†	3.83 ± 0.15*†‡
Peak work rate (W)	113 ± 7	97 ± 4*	79 ± 3*†	54 ± 4*†‡

NYHA indicates New York Heart Association functional classification; VE-VCO$_2$ slope, the slope of minute ventilation (VE)-CO$_2$ output (VCO$_2$) relationship; AT, anaerobic threshold; VO$_2$, 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.

was calculated by linear regression analysis using the values of minute ventilation and CO$_2$ output.

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

$$VD/VT = (PaCO_2 - PeCO_2)/PaCO_2 - VDM/VT,$$

where VT is tidal volume, PeCO$_2$ is mixed expired PCO$_2$ 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 PETCO$_2$ and PaCO$_2$ variables were compared by two-way ANOVA with repeated measures. Dif-

ferences 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-CO$_2$ output relationship was higher in the patients than in the control subjects, and became higher with increases in the NYHA class.

PETCO$_2$ 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). PETCO$_2$ increased during exercise in patients and control subjects. There was a significant difference in the change of PETCO$_2$ during exercise among the four groups at each time point (one way-ANOVA at each time point: rest p = 0.0016, 20W p = 0.0001, 30W p = 0.0001, AT p = 0.0001, RC p = 0.0001, Peak p = 0.0001). PETCO$_2$ was significantly lower in the cardiac patients than in the normal subjects, and the difference became more marked as the exercise work rate increased.

PETCO$_2$ was lower in the cardiac patients than in the normal subjects at the same CO$_2$ output during exercise, and decreased with increases in the NYHA class (Fig. 2). PETCO$_2$ was lower in cardiac patients than in normal
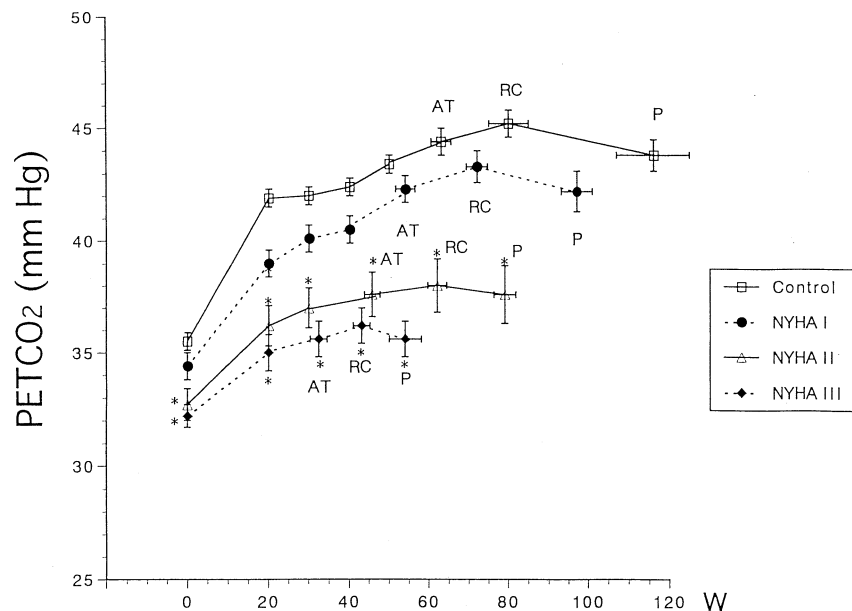

Figure 1. End-tidal CO$_2$ pressure (PETCO$_2$) at rest and during exercise according to the NYHA functional class. There was a significant difference in the change of PETCO$_2$ during exercise among the four groups at each time point (one way-ANOVA at each time point: rest p = 0.0016, 20 W p = 0.0001, 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.
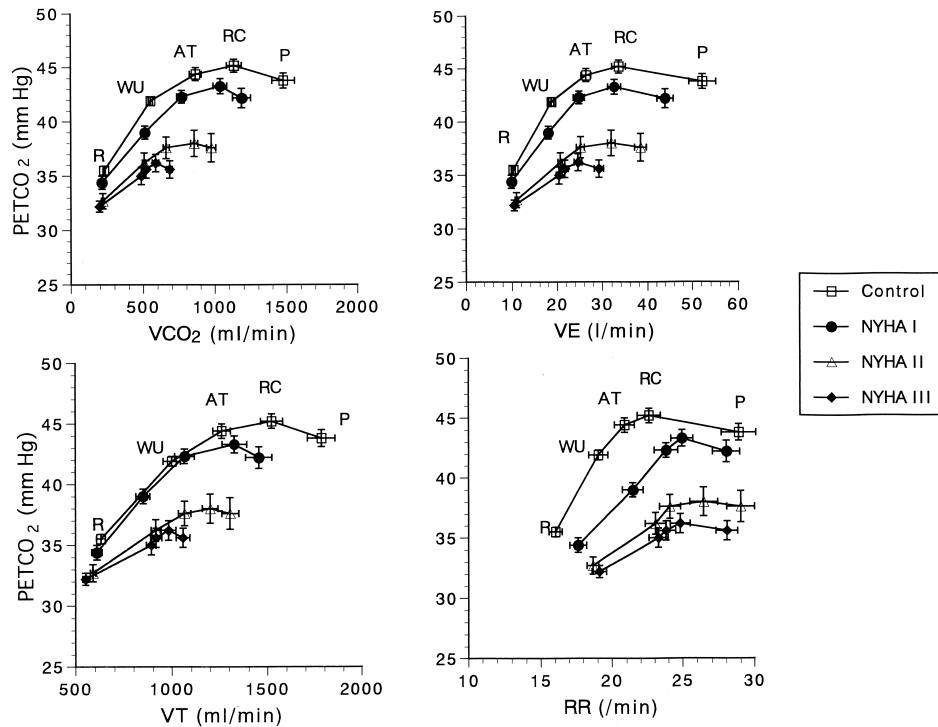
Figure 2. End-tidal CO_2 pressure ($PETCO_2$) at rest and during exercise in relation to CO_2 output ($\dot{V}CO_2$), minute ventilation ($\dot{V}E$), tidal volume (VT), and respiratory rate (RR) at rest (R), during 20 W warming-up (WU), at anaerobic threshold (AT), at respiratory compensation point (RC), and at peak exercise (P) according to the NYHA functional class. Values are mean ± SE.

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 $PETCO_2$ and cardiac index at rest and during exercise is also demonstrated in Figure 3. The relationship between $PETCO_2$ 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 $PETCO_2$ also decreased. The decrease of $PETCO_2$ was more marked in patients with severe heart failure, as indicated by their NYHA functional class.
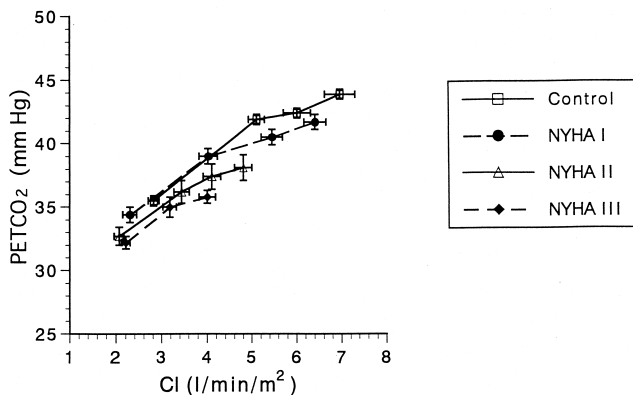
$PETCO_2$ at the respiratory compensation point correlated positively with the cardiac index at peak exercise (r = 0.582, p < 0.0001, Fig. 4). If less than 38.5 mm Hg (that is, mean–2 SD) of $PETCO_2$ at respiratory compensation point and a cardiac index of 5.11 $l/min/m^2$ at peak exercise were considered to be abnormal in the control subjects, abnormally low values of $PETCO_2$ 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
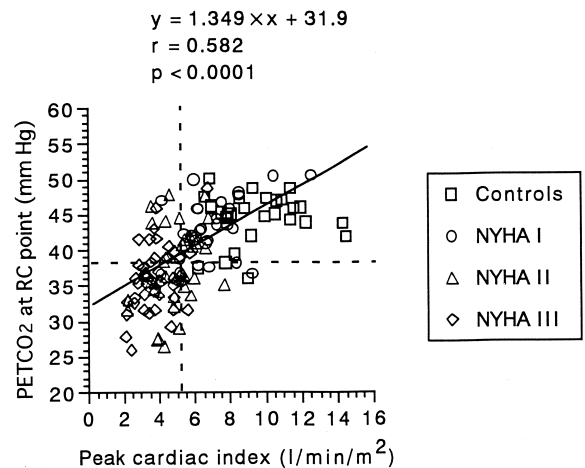

Figure 3. End-tidal CO_2 pressure ($PETCO_2$) in relation to the cardiac index (CI) at rest, at 20 W, 40 W, and 60 W during exercise according to the NYHA functional class. Values are mean ± SE.

Figure 4. Relationships of end-tidal CO_2 pressure ($PETCO_2$) at the respiratory compensation (RC) point with the cardiac index at peak exercise in 112 cardiac patients and 29 normal subjects. Dotted lines indicate mean–2SD values of $PETCO_2$ at the respiratory compensation point and the cardiac index at peak exercise in the normal control subjects.
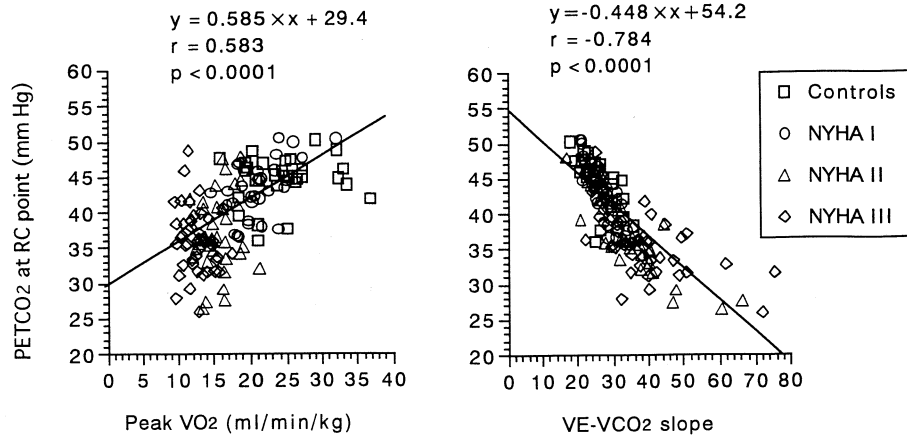
Figure 5. Relationships of end-tidal CO$_2$ pressure (PETCO$_2$) at the respiratory compensation (RC) point with O$_2$ uptake (VO$_2$) at peak exercise, or with the slope of minute ventilation-CO$_2$ output (VE-VCO$_2$ slope) in 112 cardiac patients and 29 normal subjects.

normal level of PETCO$_2$. Thus, the sensitivity and specificity of PETCO$_2$ for decreased cardiac output were 76.6% and 75.0%, respectively.

PETCO$_2$ at the respiratory compensation point correlated positively with O$_2$ uptake at peak exercise (r = 0.583, p < 0.0001, Fig. 5). Moreover, PETCO$_2$ at the respiratory compensation point was correlated with the slope of minute ventilation-CO$_2$ 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, PaCO$_2$ was similar in both groups at rest and during exercise (Fig. 6). PETCO$_2$ was lower than PaCO$_2$ at rest in both patients and control subjects, but P(a-ET)CO$_2$ 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 PaCO$_2$ and PETCO$_2$ 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, PETCO$_2$

increased above PaCO$_2$ in control subjects, but remained below PaCO$_2$ in patients. PETCO$_2$ 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).

PaO$_2$ 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 PAO$_2$ at rest or during exercise. P(A-a)O$_2$ 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,

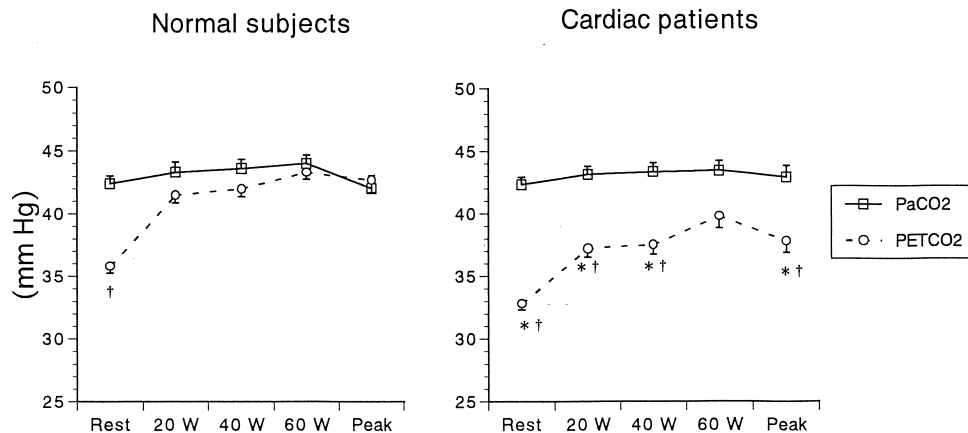**Figure 6.** End-tidal CO$_2$ pressure (PETCO$_2$) and arterial PCO$_2$ (PaCO$_2$) at rest and during exercise in 53 cardiac patients and 15 normal control subjects. There was a significant difference in the change between PaCO$_2$ and PETCO$_2$ variables and interaction with time in both the patients (variables p = 0.0001, interaction p = 0.0001, by ANOVA) and control subjects (variables p = 0.0001, interaction p = 0.0001, by ANOVA). Peak indicates peak exercise. Values are mean ± SE. *; p < 0.05 versus normal controls. †; p < 0.05 versus PaCO$_2$.
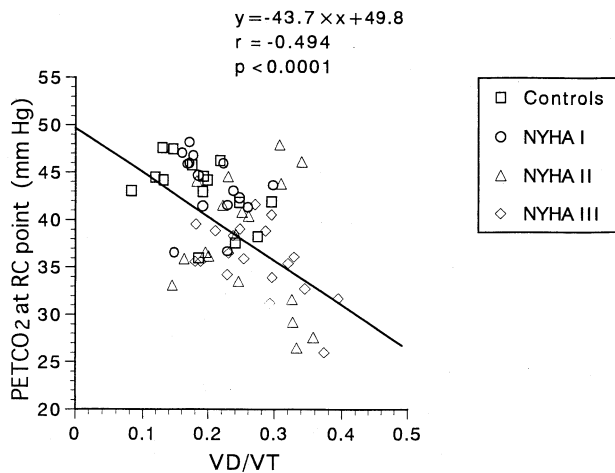
$$y = -43.7 \times x + 49.8$$
$$r = -0.494$$
$$p < 0.0001$$

Figure 7. Relationships of end-tidal CO$_2$ pressure (PETCO$_2$) 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.

86 ± 3%; NYHA I, 77 ± 3%; II, 71 ± 4%; III, 74 ± 3%; p = 0.17). PETCO$_2$ correlated weakly with %FEV1 (r = 0.236, p = 0.038), but not with %FVC (r = 0.195, p = 0.087) or the FEV1/FVC ratio (r = 0.105, p = 0.42).

To investigate whether duration of exercise influences PETCO$_2$ during exercise, 7 normal control subjects (4 men and 3 women) were asked to perform two ramp exercise tests according to a rapidly and a slowly increasing ramp protocol. The rapidly increasing protocol consisted of 1-W increments every 3 s after 4 min warmup at 20 W, and the slowly increasing protocol consisted of 1-W increments every 6 s after the same warm-up. The duration of the ramp exercise was shorter in the rapidly increasing protocol than in the slowly increasing protocol (5.87 ± 0.43 vs. 10.70 ± 0.67 min, p = 0.0002). The duration of ramp exercise did not significantly alter the values of PETCO$_2$ during exercise (at the respiratory compensation point, rapidly increasing protocol 46.2 ± 1.3 vs. slowly increasing protocol 47.3 ± 1.6 mm Hg, p = 0.61).

DISCUSSION

Summary of the Findings

PETCO$_2$ was lower at rest and during exercise in cardiac patients compared with normal subjects, and decreased in association with increases in the NYHA class. PETCO$_2$ was correlated with cardiac output during exercise, and the sensitivity and specificity of PETCO$_2$ regarding decreased cardiac output were good. PETCO$_2$ was also positively correlated with O$_2$ uptake and was negatively correlated with the slope of minute ventilation-CO$_2$ output relationship and the ratio of physiologic dead space to tidal volume. On the other hand, P(A-a)O$_2$ was similar in cardiac patients and in the normal control subjects at rest and during exercise. The present study demonstrates that PETCO$_2$ is abnormally regulated during exercise in patients with cardiac disease, and that the decrease in PETCO$_2$ is due to changes in the pulmonary circulation (pulmonary blood flow) and not in the airways.

Potential mechanisms

There was no intergroup difference in PaCO$_2$ between cardiac patients and normal subjects at rest and during exercise in the present study, which is consistent with previous findings (4). Although PaCO$_2$ was greater than PETCO$_2$ at rest in both the patients and the normal subjects, P(a-ET)CO$_2$ was greater in cardiac patients than in normal subjects at rest. During exercise, PETCO$_2$ increased in both patients and normal subjects in this study. In normal individuals, PETCO$_2$ increases because of the increased rate of CO$_2$ delivery to the lungs associated with the high rate of CO$_2$ production during exercise (30). During exhalation, the alveolar CO$_2$ pressure (PaCO$_2$) approaches the venous PaCO$_2$ because fresh air does not dilute the alveolar gas. Because PETCO$_2$ is the highest PaCO$_2$ in the alveolus during the respiratory cycle and the arterial PaCO$_2$ represents the average alveolar PaCO$_2$, PETCO$_2$ is higher than PaCO$_2$ during exercise in normal individuals. However, in the present study, decreased PETCO$_2$ with positive P(a-ET)CO$_2$ was observed in cardiac patients during exercise. Although PETCO$_2$ is almost similar to PaCO$_2$ in perfused alveoli, it is lower than PaCO$_2$ in poorly perfused or high-ventilation/perfusion (VA/Q) alveoli (22,23,30). Therefore, the greater P(a-ET)CO$_2$ 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). PETCO$_2$ 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 PETCO$_2$ at rest (35). Therefore, the inappropriate increase in cardiac output during exercise may have caused PETCO$_2$ to decrease in cardiac patients. Although Wasserman et al. (7), showed that PETCO$_2$ at peak exercise is positively correlated with peak O$_2$ uptake in patients with chronic heart failure, it has been unknown what mechanism(s), especially cardiac output, might be responsible for the decreased PETCO$_2$ in cardiac patients. On the other hand, this study clearly demonstrated that PETCO$_2$ 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 PETCO$_2$-cardiac index relationship between normal subjects and cardiac patients (Fig. 3). PETCO$_2$ 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 PETCO$_2$ during exercise, and that decreased perfusion of ventilated alveoli was a likely cause of the decreased PETCO$_2$.

Because PETCO$_2$ is also determined by the rate of CO$_2$ production during exercise (30,34), a decrease in PETCO$_2$ may reflect decreased CO$_2$ production during exercise in cardiac patients. However, PETCO$_2$ was lower in cardiac patients than in normal subjects at the same CO$_2$ output, which was almost equal to CO$_2$ production in the whole body. Therefore, the decrease in PETCO$_2$ in these patients was not due to decreased CO$_2$ production. PETCO$_2$ 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 PETCO$_2$ was not related to abnormal ventilation patterns (rapid and shallow breathing) or compensatory hyperventilation.

Minute ventilation is mainly determined by the rate of CO$_2$ production, the physiologic dead space, and the level at which PaCO$_2$ is regulated (20,22,36). Minute ventilation increases linearly with CO$_2$ output to maintain a relatively stable arterial PCO$_2$ during exercise (20,22). In the present study, the slope of minute ventilation and CO$_2$ 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, PETCO$_2$ was negatively correlated with the slope of the minute ventilation-CO$_2$ output relationship and with the ratio of physiologic dead space to the tidal volume. This study also showed that P(A-a)O$_2$ 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 PETCO$_2$ is due to changes in the pulmonary circulation and not in the airways. Therefore, the decreased PETCO$_2$ 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. PETCO$_2$ 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, PETCO$_2$ 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 PETCO$_2$ as a means to evaluate cardiac output reserve are valid only for cardiac patients. Because PETCO$_2$ 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 PETCO$_2$ at rest and during exercise compared with normal subjects. PETCO$_2$ was correlated with cardiac output during exercise, and the sensitivity and specificity of PETCO$_2$ regarding decreased cardiac output were good. PETCO$_2$ was also correlated with the slope of the relationship between minute ventilation and CO$_2$ output, and the ratio of physiologic dead space to the tidal volume. PETCO$_2$ may be a new marker of ventilatory abnormalities that reflects impaired cardiac output response to exercise in cardiac patients.

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