Attenuation of hypercapnic carbon dioxide chemosensitivity after postinfarction exercise training: possible contribution to the improvement in exercise hyperventilation

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Objective: To elucidate the responsible mechanisms of increased slope of minute ventilation relative to carbon dioxide production ($\dot{V}_E/\dot{V}_{CO_2}$) during exercise after acute myocardial infarction without overt signs of heart failure, patients who had an acute myocardial infarction were examined after participating in a three month supervised exercise training programme.

Design: Exercise testing, hypercapnic CO_2 chemosensitivity measurement (rebreathing method), and pulmonary function test were repeated at entry and after three months in 50 acute myocardial infarction patients with neither symptoms nor signs of heart failure who completed the training programme. Ten patients who performed initial in-hospital training served as controls.

Results: Age, peak oxygen uptake, left ventricular ejection fraction, CO_2 chemosensitivity, respiratory parameters (percentage of predicted normal vital capacity (%VC), forced expiratory volume in one second, and carbon monoxide transfer factor (%Tlco)) were all significantly correlated with $\dot{V}_E/\dot{V}_{CO_2}$ slope. Multivariate regression analysis showed that age ($\beta = 0.29$, $p = 0.01$), %Tlco ($\beta = -0.27$, $p = 0.01$), and CO_2 chemosensitivity ($\beta = 0.49$, $p < 0.001$) were independent determinants of $\dot{V}_E/\dot{V}_{CO_2}$ slope. After three months, there was no significant change in these parameters in the control group. Peak oxygen uptake, %Tlco, and %VC and attenuation in CO_2 chemosensitivity increased significantly in the training group. The $\dot{V}_E/\dot{V}_{CO_2}$ slope decreased marginally ($p = 0.11$). The changes in $\dot{V}_E/\dot{V}_{CO_2}$ slope were correlated only with those in CO_2 chemosensitivity ($r = 0.50$, $p < 0.001$).

Conclusion: After acute myocardial infarction, exercise hyperventilation is seen in association with aging, enhanced hypercapnic CO_2 chemosensitivity, and reduced Tlco, even in the absence of overt heart failure. The correlation of $\dot{V}_E/\dot{V}_{CO_2}$ attenuation after training with the reduction in CO_2 chemosensitivity suggests that exercise training may reduce increased $\dot{V}_E/\dot{V}_{CO_2}$ slope, at least partially by reducing CO_2 chemosensitivity.

Exercise hyperventilation characteristic of patients with chronic heart failure may contribute to their exercise intolerance. It can be estimated by an increased minute ventilation relative to carbon dioxide (CO_2) production ($\dot{V}_E/\dot{V}_{CO_2}$ slope), which is known to be related to the severity of heart disease. Furthermore, this index has recently received increasing attention since it is a powerful prognostic marker independent of peak oxygen uptake ($\dot{V}_{O_2}$) and left ventricular function.^{1,2} Several factors such as inefficient ventilation (perfusion-ventilation mismatch, rapid-shallow respiratory pattern),³⁻⁹ alteration in CO_2 chemosensitivity,¹⁰ ergoreflex overactivation,¹¹⁻¹⁴ and possibly reduced alveolar-capillary membrane diffusing capacity (carbon monoxide transfer factor (Tlco))^{15,16} are thought to be responsible for exercise hyperventilation, although the details remain unsettled.

Intriguingly, exercise training, the most potent means of improving exercise intolerance, ameliorates exercise hyperventilation in patients with chronic heart failure.^{17,18} Although exercise hyperventilation has been believed to be characteristic of chronic heart failure, several studies have suggested that the presence of chronic heart failure is not necessarily a prerequisite for this phenomenon.^{19,20} We also have recently reported that, even in the absence of overt heart failure, some patients with acute myocardial infarction exhibited an increased $\dot{V}_E/\dot{V}_{CO_2}$ slope, which was attenuated after an exercise training programme.²¹ The underlying mechanism(s) for the above results remain undetermined, however. Because it is

unlikely that these patients have perfusion-ventilation mismatch or rapid-shallow ventilation pattern during exercise, and because ergoreflex overactivation, probably caused by prolonged inactivity, does not appear to occur in these patients, we can postulate that these results may be associated with alteration in CO_2 chemosensitivity through unknown mechanisms such as excessive sympathetic tone, which has been observed in these patients and has been implicated as a factor of accelerated ventilation.²²⁻²⁴ We therefore measured exercise ventilation, hypercapnic CO_2 chemosensitivity, and respiratory function, including Tlco, before and after a three month exercise training programme in patients with acute myocardial infarction. The purpose of the present study was twofold: firstly, to evaluate the determinants of an increased $\dot{V}_E/\dot{V}_{CO_2}$ slope in patients with acute myocardial infarction but with neither symptoms nor signs of heart failure; and, secondly, to examine the hypothesis that alteration in CO_2 chemosensitivity contributes to the attenuation of the $\dot{V}_E/\dot{V}_{CO_2}$ slope after exercise training.

Abbreviations: FEV₁, forced expiratory volume in one second; LVEF, left ventricular ejection fraction; Tlco, carbon monoxide transfer factor; VC, vital capacity; $\dot{V}_E/\dot{V}_{CO_2}$, minute ventilation relative to carbon dioxide production; $\dot{V}_{O_2}$, oxygen uptake

Table 1 Patient characteristics

	Group C (n=10)	Group T _{low} (n=27)	Group T _{high} (n=23)
Age (years)	57 (13)	58 (11)	63 (7)
Men/women	7/3	22/5	22/1
Ejection fraction (%)	46 (9)	45 (8)	41 (10)
Forrester's subset II or greater	2	3	3
Drug administration			
ACE inhibitors	8 (80%)	16 (59%)	14 (61%)
β Blockers	4 (40%)	2 (7%)	7 (30%)
Digoxin	0 (0%)	0 (0%)	3 (13%)
Spirometry			
VC (%predicted)	105 (13)	102 (12)	97 (13)
FEV ₁ (%predicted)	82 (6)	86 (11)	80 (11)
TlCO (%predicted)	102 (17)	105 (17)	96 (26)
Peak $\dot{V}O_2$ (ml/kg/min)	24 (5)	23 (5)	19 (4)*†
$\dot{V}E/\dot{V}CO_2$ slope	30 (10)	25 (3)*	35(5)*†

Data are mean (SD) or number of patients. *p<0.05 v control; †p<0.05 v group T_{low} (pretraining slope of minute ventilation relative to carbon dioxide production ($\dot{V}E/\dot{V}CO_2$) <30). ACE, angiotensin converting enzyme; Group C, control group; FEV₁, forced expiratory volume in one second; Peak $\dot{V}O_2$, peak oxygen uptake; T_{high}, pretraining $\dot{V}E/\dot{V}CO_2 \geq 30$; TlCO, carbon monoxide transfer factor; VC, vital capacity.

METHODS

Study population

Among patients who were admitted to the coronary care unit of our hospital for the diagnosis of acute myocardial infarction, 60 consecutive patients were enrolled into this study. They subsequently (during hospitalisation) participated in the supervised exercise training programme at our rehabilitation institute and consented to take part in the study (table 1). The mean (SD) interval between the onset of myocardial infarction and entry into the programme was 13 (4) days (median 13 days). Forty three of the 60 patients (72%) received revascularisation in the acute phase of infarction. In the acute phase, eight patients had transient haemodynamic impairment defined as a grade of subset II or greater according to the Forrester classification. At entry, no patients had postinfarct angina, symptoms of heart failure, or clinical evidence of residual ischaemia during exercise testing. Left ventricular ejection fraction (LVEF) determined by contrast left ventriculography before discharge was 44 (9)% (range 19–59%). There were five patients with low LVEF of < 30% but all patients, including these five, had neither symptoms nor signs of heart failure. Only two patients had a previous myocardial infarction. Patients with primary lung disease or vascular or orthopaedic problems of the lower extremities that precluded exercise training were excluded from the study.

Fifty patients who completed the supervised exercise training programme three to five times a week for three months were assigned to the training group. The other 10 patients, who performed the initial low intensity exercise during admission (two weeks) but discontinued the training after hospital discharge, served as controls (group C). The reason for the early discontinuation was not a medical problem in any patient of group C (reasons were occupational or social problems and living a long distances from our institute). No patients in group C engaged in regular exercise after discharge. Because our previous study²¹ had indicated that attenuation of the $\dot{V}E/\dot{V}CO_2$ slope after exercise training was found only in patients with increased baseline (pretraining) values of $\dot{V}E/\dot{V}CO_2$, we divided 50 patients into two subgroups according to the value of $\dot{V}E/\dot{V}CO_2$ measured at pretraining exercise testing. Group T_{low} consisted of 27 patients with pretraining $\dot{V}E/\dot{V}CO_2 < 30$ and group T_{high} of 23 patients with pretraining $\dot{V}E/\dot{V}CO_2 \geq 30$. The cut off value of $\dot{V}E/\dot{V}CO_2$ (= 30) was determined based on our previous study.²¹ Drug regimens were not altered throughout the study.

Symptom limited exercise testing, pulmonary function testing, and measurement of CO₂ chemosensitivity were repeated at entry into the training programme and three months later in all 60 subjects. The three tests were performed on the same day: exercise testing was followed by pulmonary function testing and measurement of CO₂ chemosensitivity after at least 30 minutes of rest. The first and second examinations were conducted 19 (14) days (median 17 days) and 111 (23) days (median 108 days) after the onset of myocardial infarction, respectively. All subjects gave written informed consent for the study.

Exercise test with gas analysis

Symptom limited exercise testing with simultaneous gas analysis (AE-280, Minato Medical Science, Osaka, Japan) was performed on an electronically braked ergometer (Examiner 400, Lode, Groningen, The Netherlands) in the upright position. After unloaded bicycling (0 W) for one minute, exercise intensity was increased in a ramp fashion (15 W/min) until exhaustion in terms of dyspnoea or fatigue. Subjects were constantly encouraged to make their maximal efforts. ECGs were continuously monitored throughout the test. Arterial blood pressure was measured by cuff sphygmomanometer every minute during exercise and 1–2 minutes during recovery. Peak $\dot{V}O_2$ was determined as the averaged $\dot{V}O_2$ over 18 seconds before the termination of exercise. The slope of the linear regression relating minute ventilation to CO₂ output between the beginning of the exercise and the respiratory compensation point was used as the index of the ventilatory response to exercise ($\dot{V}E/\dot{V}CO_2$ slope).^{7, 8}

Pulmonary function test

Standard measurements of forced expiratory volume in one second (FEV₁) and vital capacity (VC) were made with FUDAC-70 (Fukuda Denshi Co Ltd, Tokyo, Japan). Pulmonary carbon monoxide diffusion (TlCO) was measured using a single breath technique. These data were expressed as a percentage of predicted normal values (%FEV₁, %VC, and %TlCO) on the basis of standard nomograms incorporating age, sex, height, and weight.²⁵

CO₂ chemosensitivity measurement

According to the CO₂ rebreathing method reported by Read,²⁶ we measured CO₂ chemosensitivity as follows. Breath by breath minute ventilation and end tidal CO₂ concentration were measured by the gas analyser system (AE-280, Minato Medical Science), and the data were stored in the computer hard disk for later analysis. We used custom made equipment consisting of a mouthpiece, an airway tube with a one way valve, and a 6 l bag, which initially contained a gas mixture of 7% CO₂ in 93% O₂. After the subject quietly breathed room air for at least three minutes, a one way valve was switched for the rebreathing procedure. As the subject's expired gas was collected into the bag, the CO₂ concentration of the inspired gas from the bag was gradually increased, resulting in hyperventilation through stimulation of the hypercapnic chemoreceptor. Although subjects were asked to continue the procedure for four minutes, the test was terminated earlier if subjects had too strong a sensation of dyspnoea to continue the rebreathing or if end tidal CO₂ concentration exceeded 10%. CO₂ chemosensitivity was defined as the slope of the increase in minute ventilation relative to the increase in end tidal CO₂ concentration and was expressed in terms of l/min/mm Hg. Because CO₂ chemosensitivity reported by others varies considerably,^{10–27, 28} we examined age matched healthy subjects (n = 9, 62 (8) years old) without any cardiovascular disease.

Exercise training programme

Initial early sessions of the exercise training programme were conducted individually under close supervision for approximately the first two weeks during hospitalisation. Patients

Figure 1 Relation between the slope of minute ventilation relative to carbon dioxide production ($\dot{V}E/\dot{V}CO_2$) and CO_2 chemosensitivity, and relations between the $\dot{V}E/\dot{V}CO_2$ slope and spirometric parameters in 60 patients under the baseline conditions. Three pulmonary function variables were all weakly but significantly correlated with the $\dot{V}E/\dot{V}CO_2$ slope during exercise (percentage of predicted normal carbon monoxide transfer factor (% $Tlco$), $r = -0.33$, $p = 0.01$; percentage of predicted normal vital capacity (% VC), $r = -0.28$, $p = 0.03$; and percentage of predicted forced expiratory volume in one second (% $FEV_{1.0}$), $r = -0.30$, $p = 0.02$). CO_2 chemosensitivity was relatively strongly correlated with the $\dot{V}E/\dot{V}CO_2$ slope ($r = 0.62$, $p < 0.001$).

performed brisk walking on an indoor track and light bicycling at a heart rate of 20–30 beats/min above the resting rate. Subsequent standard training programme for 50–90 minutes consisted of bicycling and aerobic exercise (calisthenics, stretching, dancing) under the guidance of an exercise trainer. In this late phase, the exercise intensity was maintained at a heart rate of 50–60% of heart rate reserve, calculated from the resting and peak heart rate during the symptom limited exercise test. During each session, we continuously monitored the ECG to maintain each patient's individual training heart rate.

Statistical analysis

Data are expressed as mean (SD). We conducted linear univariate regression analysis to assess the significance of association between $\dot{V}E/\dot{V}CO_2$ and its possible correlates. To determine which of these factors were significant independent determinants of the $\dot{V}E/\dot{V}CO_2$ slope, we used multivariate regression analysis. Between group analysis was done by one way analysis of variance with Scheffé's test for multiple comparisons. The paired t test was used for comparisons within a group. Data were considered to be significantly different if $p < 0.05$ was observed.

RESULTS

At baseline, there was no significant difference between the training group (groups T_{High} and T_{Low}) and group C with respect to age, male to female ratio, LVEF, incidence of Forrester's subset II or greater, or use of drugs (angiotensin converting

enzyme inhibitors, β blockers, and digoxin), spirometric parameters, or peak $\dot{V}O_2$ (table 1). However, when the three groups were compared separately (groups T_{High} , T_{Low} , and C), peak $\dot{V}O_2$ in group T_{High} was significantly lower than that in group T_{High} or group C (both $p < 0.05$). Trends towards higher age, greater male to female ratio, lower LVEF, and more frequent use of digoxin were also observed in group T_{High} but these differences did not reach significance.

In nine age matched normal healthy subjects, hypercapnic CO_2 chemosensitivity was estimated to be 1.4 (0.4) l/min/mm Hg. This value was quite similar to that of group C (1.3 (1.0) l/min/mm Hg) and group T_{Low} (1.3 (0.5) l/min/mm Hg) under baseline conditions (at entry into the exercise training programme). Only group T_{High} (2.0 (0.7) l/min/mm Hg) had higher than normal values of CO_2 chemosensitivity ($p < 0.05$).

Baseline relation of variables of pulmonary function and CO_2 chemosensitivity to $\dot{V}E/\dot{V}CO_2$ slope

In the 60 patients under the baseline conditions, three pulmonary function variables were all weakly but significantly correlated with the $\dot{V}E/\dot{V}CO_2$ slope during exercise (% $Tlco$, $r = -0.33$, $p = 0.01$; % VC , $r = -0.28$, $p = 0.03$; % $FEV_{1.0}$, $r = -0.30$, $p = 0.02$) (fig 1), while CO_2 chemosensitivity was relatively strongly correlated with the $\dot{V}E/\dot{V}CO_2$ slope ($r = 0.62$, $p < 0.001$). Peak $\dot{V}O_2$ ($r = -0.53$, $p < 0.001$), age ($r = 0.57$, $p < 0.001$), and LVEF ($r = -0.29$, $p = 0.03$) were also significantly correlated with the $\dot{V}E/\dot{V}CO_2$ slope. $\dot{V}E/\dot{V}CO_2$ slope was not significantly affected by the presence or absence of acute

Table 2 Changes in exercise parameters, CO₂ chemosensitivity and spirometric variables before and after a three month exercise training programme

	Group C		Group T _{Low}		Group T _{High}	
	Before	After	Before	After	Before	After
Exercise testing						
Peak $\dot{V}O_2$ (ml/kg/min)	24 (5)	25 (6)	23 (5)	25 (6)**	19 (4)	21 (3)***
$\dot{V}E/\dot{V}CO_2$ slope	30 (10)	29 (8)	25 (3)	26 (4)	35 (5)	33 (6)*
CO ₂ chemosensitivity (l/min/mm Hg)	1.3 (1.0)	1.4 (1.3)	1.3 (0.5)	1.0 (0.4)***	2.0 (0.7)	1.6 (0.7)***
Spirometry						
VC (%predicted)	105 (13)	107 (18)	102 (12)	104 (12)	97 (13)	101 (13)*
FEV ₁ (%predicted)	82 (6)	81 (7)	86 (11)	86 (14)	80 (11)	81 (12)
Tlco (%predicted)	102 (17)	108 (17)	105 (17)	115 (21)***	96 (26)	100 (29)

*p<0.05; **p<0.01; ***p<0.001 v baseline.

phase haemodynamic impairment (subset II or greater of Forrester class). The multivariate regression model including the above six significant variables with $p < 0.05$ showed that age, %Tlco, and CO₂ chemosensitivity were significant independent variables; however, the association was most evident for CO₂ chemosensitivity ($\beta = 0.49$, $p < 0.0001$) compared with age ($\beta = 0.29$, $p = 0.007$) and %Tlco ($\beta = -0.27$, $p = 0.008$). These results suggest that CO₂ chemosensitivity has an important role in determining the $\dot{V}E/\dot{V}CO_2$ slope early after acute myocardial infarction, although multiple factors seem to be involved in the pathogenesis.

Changes in peak $\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ slope

Peak $\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ slope did not change significantly in group C at the exercise testing after three months (table 2). In 50 patients who completed the exercise training programme,

peak $\dot{V}O_2$ increased significantly from 21 (5) to 23 (5) ml/min/kg after the three month training programme ($p < 0.001$). This improvement was similar in both subgroups ($p < 0.01$ for group T_{Low}, $p < 0.001$ for group T_{High}). The $\dot{V}E/\dot{V}CO_2$ slope was significantly attenuated in group T_{High} ($p < 0.001$) but not in group T_{Low} after three months compared with the baseline value. The changes in $\dot{V}E/\dot{V}CO_2$ slope for the whole group (30 (6.4) to 29 (6.0)) did not reach significance ($p = 0.11$).

Changes in CO₂ chemosensitivity and pulmonary function parameters

After three months, CO₂ chemosensitivity in group C remained unchanged (1.3 (1.0) to 1.4 (1.3) /min/mm Hg, NS), while that in the training group was significantly attenuated from 1.6 (0.7) to 1.3 (0.6) l/min/mm Hg ($p < 0.001$) in the whole

Figure 2 Relation between changes (Δ) in the $\dot{V}E/\dot{V}CO_2$ slope and in CO₂ chemosensitivity, and between changes in the $\dot{V}E/\dot{V}CO_2$ slope and in spirometric parameters in the training group ($n = 50$). Changes in the $\dot{V}E/\dot{V}CO_2$ slope after three months were significantly correlated with changes in CO₂ sensitivity ($r = 0.50$, $p < 0.001$) but not with changes in spirometric parameters.

Figure 3 Relation between changes in the $\dot{V}E/\dot{V}CO_2$ slope and in CO_2 chemosensitivity in the training subgroups (pretraining $\dot{V}E/\dot{V}CO_2 < 30$ (group T_{Low}, left) and pretraining $\dot{V}E/\dot{V}CO_2 \geq 30$ (T_{High}, right)). Changes in the $\dot{V}E/\dot{V}CO_2$ slope were significantly correlated with changes in CO_2 chemosensitivity only in group T_{High} ($r = 0.64$, $p < 0.002$), not in group T_{Low} ($r = 0.33$, $p = 0.10$).

group. This attenuation was significant in both subgroups ($p < 0.001$ for group T_{Low}, $p < 0.001$ for group T_{High}).

Among the three pulmonary function parameters, in the training group %VC and %Tlco increased significantly (both $p < 0.05$), while %FEV₁ remained unchanged. When analysed separately within each subgroup, significant changes were observed in %VC only in group T_{High} ($p < 0.05$) and in %Tlco only in group T_{Low} ($p < 0.001$). None of these three parameters was significantly different in group C.

Changes in $\dot{V}E/\dot{V}CO_2$ slope versus changes in CO_2 chemosensitivity and pulmonary function parameters

In the 50 patients in the training group, the changes from baseline in the $\dot{V}E/\dot{V}CO_2$ slope after three months were significantly correlated with changes in CO_2 sensitivity ($r = 0.50$, $p < 0.001$). No such significant correlation was found for any of three pulmonary function variables (fig 2). When analysed in the subgroups, the changes in the $\dot{V}E/\dot{V}CO_2$ slope were significantly correlated with changes in CO_2 chemosensitivity only in group T_{High} ($r = 0.64$, $p < 0.002$) but not in group T_{Low} ($r = 0.33$, $p = 0.10$) (fig 3). These findings reasonably support the idea that attenuation in CO_2 chemosensitivity may have a central role in improving the exercise hyperventilation (that is, increased $\dot{V}E/\dot{V}CO_2$ slope) seen in patients after acute myocardial infarction.

DISCUSSION

Our previous study showed that an increased $\dot{V}E/\dot{V}CO_2$ slope (≥ 30) during exercise is seen in a substantial proportion (over 40%) of patients with acute myocardial infarction, in whom the increased slope was attenuated after three months' exercise training.²¹ The present study has confirmed these results in a separate population. We aimed at exploring the mechanisms responsible for the above hitherto unknown issues and obtained the following results. (1) Among the three subgroups, only group T_{High} with increased $\dot{V}E/\dot{V}CO_2$ relative to baseline had higher than normal CO_2 chemosensitivity. (2) Age, Tlco, and CO_2 chemosensitivity were independently related to the baseline $\dot{V}E/\dot{V}CO_2$ slope. (3) Regardless of the baseline level, CO_2 chemosensitivity was significantly attenuated after exercise training. Changes in the $\dot{V}E/\dot{V}CO_2$ slope after exercise training were significantly correlated only with changes in CO_2 chemosensitivity, not with any of the other parameters. These results suggest that, even in the absence of overt heart failure, $\dot{V}E/\dot{V}CO_2$ slope is increased in a significant proportion of postinfarct patients in association with aging, reduced Tlco, and enhanced CO_2 chemosensitivity, and that

the increased $\dot{V}E/\dot{V}CO_2$ slope may be reduced by exercise training, at least partially, through the attenuation of CO_2 chemosensitivity. To our knowledge, in patients with heart disease, the possible role of CO_2 chemosensitivity in the improvement in increased $\dot{V}E/\dot{V}CO_2$ slope after exercise training has not been shown elsewhere.

Mechanisms for increased $\dot{V}E/\dot{V}CO_2$ slope

Although the detailed mechanisms underlying the increased $\dot{V}E/\dot{V}CO_2$ slope during exercise are still debated, multiple factors appear to be related to this phenomenon. Traditionally, these include a ventilation-perfusion mismatch underlying a limited increase in cardiac output and an increase in pulmonary dead space caused by rapid and shallow exercise breathing caused by decreased lung compliance.³⁻⁹ However, a normal or near normal $\dot{V}E/\dot{V}CO_2$ slope is not uncommon in patients with the most severe left ventricular dysfunction, such as candidates for cardiac transplantation. Conversely, the $\dot{V}E/\dot{V}CO_2$ slope is often greatly increased in some patients with relatively preserved left ventricular function and no pulmonary disease. This notion is compatible with the wide ranges of $\dot{V}E/\dot{V}CO_2$ slope in previous studies examining patients with severe heart failure.^{2-21, 29} These findings suggest that exercise hyperventilation may be caused not only by severely depressed left ventricular function and inefficient ventilation (rapid-shallow respiratory pattern caused by decreased lung compliance) but also by other mechanisms such as changes in exaggerated ergoreflex activity¹¹⁻¹⁴ or alterations in the control of ventilation during exercise. Our results suggest that in cardiac patients the presence of chronic heart failure is not necessarily a prerequisite for increased $\dot{V}E/\dot{V}CO_2$ slope.

The present study has shown that, in patients after acute myocardial infarction, the $\dot{V}E/\dot{V}CO_2$ slope increases in association with aging, decreased Tlco, and enhanced CO_2 chemosensitivity. Among these three factors, enhanced CO_2 chemosensitivity seems to be the most potent determinant. The increase in $\dot{V}E/\dot{V}CO_2$ slope with aging was reported in healthy subjects.³⁰ Reduction of Tlco is well known in chronic heart failure.^{15, 16, 31} In the study by Guazzi and colleagues³¹ in which enalapril improved reduced Tlco in patients with chronic heart failure, changes in the ratio of dead space to tidal volume (a major determinant of the $\dot{V}E/\dot{V}CO_2$ slope) with enalapril were closely related to changes in Tlco. This may be in keeping with our finding that reduction of Tlco is a weak but significant independent determinant of the $\dot{V}E/\dot{V}CO_2$ slope in our patients; however, changes in Tlco after three months were not associated with changes in the $\dot{V}E/\dot{V}CO_2$ slope.

In our patients, the $\dot{V}E/\dot{V}CO_2$ slope was relatively strongly correlated with peak $\dot{V}O_2$, similar to reports from studies in patients with heart failure.² A weak but significant correlation between $\dot{V}E/\dot{V}CO_2$ slope and LVEF, which is not necessarily seen in chronic heart failure, may be explained by the wider distribution of LVEF (19–59%) in our population.

$\dot{V}E/\dot{V}CO_2$ slope in patients with acute myocardial infarction

Although, as described above, several factors should contribute to the increased $\dot{V}E/\dot{V}CO_2$ slope in patients after myocardial infarction but without chronic heart failure, enhanced CO₂ chemosensitivity seems to be the most plausible mechanism. If this is the case, which mechanism can explain the enhanced CO₂ chemosensitivity in these patients? Although our study cannot explain it, it is conceivable that activation of the sympathetic nervous system after acute myocardial infarction enhances CO₂ chemosensitivity, which in turn increases the $\dot{V}E/\dot{V}CO_2$ slope. These patients are known to have heightened sympathetic tone,^{32,33} which is reported to increase ventilation,^{22–24} possibly by activation of the chemoreceptor. Another possible explanation is that an exaggerated muscle ergoreflex occurring with chronic physical deconditioning may be related to chemosensitivity activation. Further studies are necessary to confirm these issues.

Effects of exercise training

Given the importance of the contribution of enhanced CO₂ chemosensitivity to the increased $\dot{V}E/\dot{V}CO_2$ slope, one can suppose that some manipulations to reduce CO₂ chemosensitivity would improve the $\dot{V}E/\dot{V}CO_2$ slope, leading to an amelioration of breathlessness during exercise. A study by Chua and colleagues³⁴ examined this possibility with short term administration of dihydrocodeine. Of interest, the suppression of chemosensitivity with this agent was associated with a reduction of the $\dot{V}E/\dot{V}CO_2$ slope and an improvement in exercise tolerance (peak $\dot{V}O_2$) and sensation of dyspnoea at a given work rate.³⁴ On the other hand, it is well established that chronic physical training attenuates increased $\dot{V}E/\dot{V}CO_2$ slope in patients with chronic heart failure,^{17,18} whereas the $\dot{V}E/\dot{V}CO_2$ slope is shown to remain unchanged in normal subjects,³⁵ suggesting that the $\dot{V}E/\dot{V}CO_2$ slope may be altered only when the baseline level is increased. These findings are in agreement with our results—that is, the $\dot{V}E/\dot{V}CO_2$ slope was attenuated only in group T_{high} with the increased baseline level of $\dot{V}E/\dot{V}CO_2$ slope.

Our finding that changes in the $\dot{V}E/\dot{V}CO_2$ slope after exercise training were correlated only with changes in CO₂ chemosensitivity supports the notion that attenuation of CO₂ chemosensitivity may have an important role in improving exercise hyperventilation. However, the causality of this relation remains to be solved. Unknown beneficial effects produced by chronic exercise, such as improvement of the activated neurohumoral systems, may directly influence both of these two changes. In the literature, there are few data showing exercise training induced attenuation of CO₂ chemosensitivity in cardiac patients. Although this issue has not yet been fully established even in the normal subjects,³⁶ the prevailing thought is that endurance training may attenuate CO₂ chemosensitivity.

Despite the presence of acute myocardial infarction, the mean values of CO₂ chemosensitivity in group C and group T_{low} were comparable with the mean value measured in healthy subjects. Only group T_{high} had increased CO₂ chemosensitivity. The CO₂ chemosensitivity values in healthy subjects were somewhat lower than previously reported by other studies but were similar to the value reported by Yamamoto and colleagues.³⁷ Chemosensitivity is known to be lower in the elderly than in the younger subjects³⁸ and chemosensitivity varies considerably between individual subjects, which may have affected our results.

Clinical implications

Exercise training induced improvement of exercise hyperventilation may alleviate patient's dyspnoea during daily activities, as well as of exercise performance in patients with heart failure. The well established benefits of exercise training on exercise performance and quality of life in coronary artery disease may be partly brought about by the improvement in exercise hyperventilation. Exercise training has various benefits not only in the functional status of the peripheral organs but also in the regulation of the cardiocirculatory system, such as that seen by an improvement in autonomic imbalance (enhanced sympathetic drive and attenuated parasympathetic tone). It is possible that a similar central alteration of the control system of ventilation improves exercise hyperventilation, leading to amelioration of symptoms.

Study limitations

Several potential limitations of the present study should be considered. First, the present study was not designed as a randomised, controlled trial; the patients assigned to the control group (group C) underwent initial low grade exercise training during hospitalisation. The well established various benefits of a postinfarct exercise training programme could not ethically allow us to design the study in such a fashion. Although the training group and group C were well matched for all of the baseline parameters and none of the parameters changed significantly in group C after three months, this potential selection bias should be noted. The small number of patients in this group C should be recognised as one limitation of the study.

Although we defined the cut off value of 30 as an increased $\dot{V}E/\dot{V}CO_2$ slope according to our previous study, there is no consensus regarding this issue. Because multiple factors including aging, sex, and physical conditioning are likely to affect this value, its validity needs to be confirmed by further investigation.

To measure hypercapnic CO₂ chemosensitivity, we used the rebreathing method, which estimates both central and peripheral CO₂ chemosensitivity. Although both may have clinically important implications, we almost exclusively estimated the former because the peripheral hypercapnic chemosensitivity is known to be very small and negligible under the high oxygen concentration.^{39,40}

Although our patients generally had preserved LVEF, several patients had a low LVEF: five patients had LVEF < 30%, for example. Thus, we cannot completely exclude the possibility that our population may have included a number of patients with no overt but latent heart failure, especially in group T_{high}, which trended towards a lower LVEF and a significantly reduced peak $\dot{V}O_2$ compared with the other two groups. The lack of a universally accepted definition of heart failure is a problem; however, no patients with any signs or symptoms of heart failure were included in the study. Furthermore, when we reanalysed the data after excluding these five patients, the statistical results were exactly the same as those presented, supporting the idea that inclusion of patients with latent heart failure did not distort our results.

Conclusion

The present study indicated that, in patients with acute myocardial infarction, exercise hyperventilation as indicated by increased $\dot{V}E/\dot{V}CO_2$ slope during exercise occurs in association with aging, reduced Tlco, and hypercapnic CO₂ chemosensitivity. Among these three factors, chemosensitivity seems to be the most potent determinant of the abnormality. A subsequent three month supervised exercise training programme attenuates the increased $\dot{V}E/\dot{V}CO_2$ slope, at least partially, through the reduction of hypercapnic CO₂ chemosensitivity. We studied patients with acute myocardial infarction and no overt heart failure and thus cannot extrapolate these results to

patients with chronic heart failure. However, our results may provide insight into the understanding of the responsible mechanism for exercise hyperventilation and exercise training induced beneficial effects in cardiac patients.

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