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 (\( \dot{V}_{\text{E}}/\dot{V}_{\text{CO}_2} \)) production (\( \dot{V}_{\text{E}}/\dot{V}_{\text{CO}_2} \) 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 (\( \dot{V}_{\text{O}_2} \)).

Several factors such as inefficient ventilation (perfusion–ventilation mismatch, rapid–shallow respiratory pattern), alterations in \( \dot{V}_{\text{E}}/\dot{V}_{\text{CO}_2} \) slope. Multivariate regression analysis showed that age \( (\beta = 0.29, p = 0.01) \), %TLCO \( (\beta = -0.27, p = 0.01) \), and \( \dot{V}_{\text{O}_2} \) chemosensitivity \( (\beta = 0.49, p < 0.001) \) were independent determinants of \( \dot{V}_{\text{E}}/\dot{V}_{\text{CO}_2} \) 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 \( \dot{V}_{\text{O}_2} \) chemosensitivity increased significantly in the training group. The \( \dot{V}_{\text{E}}/\dot{V}_{\text{CO}_2} \) slope decreased marginally \( (p = 0.11) \). The changes in \( \dot{V}_{\text{E}}/\dot{V}_{\text{CO}_2} \) slope were correlated only with those in \( \dot{V}_{\text{O}_2} \) chemosensitivity \( (r = 0.50, p < 0.001) \).

Conclusion: After acute myocardial infarction, exercise hyperventilation is seen in association with aging, enhanced hypercapnic \( \dot{V}_{\text{E}}/\dot{V}_{\text{CO}_2} \) chemosensitivity, and reduced TlCO even in the absence of overt heart failure. The correlation of \( \dot{V}_{\text{E}}/\dot{V}_{\text{CO}_2} \) attenuation after training with the reduction in \( \dot{V}_{\text{O}_2} \) chemosensitivity suggests that exercise training may reduce increased \( \dot{V}_{\text{E}}/\dot{V}_{\text{CO}_2} \) slope, at least partially by reducing \( \dot{V}_{\text{O}_2} \) chemosensitivity.

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

T Tomita, H Takaki, Y Hara, F Sakamaki, T Satoh, S Takagi, Y Yasumura, N Aihara, Y Goto, K Sunagawa

Objective: To elucidate the responsible mechanisms of increased slope of minute ventilation relative to carbon dioxide production (\( \dot{V}_{\text{E}}/\dot{V}_{\text{CO}_2} \)) 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 inhospital training served as controls.

Results: Age, peak oxygen uptake, left ventricular ejection fraction, \( \dot{V}_{\text{O}_2} \) 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 \( \dot{V}_{\text{E}}/\dot{V}_{\text{CO}_2} \) slope. Multivariate regression analysis showed that age \( (\beta = 0.29, p = 0.01) \), %TLCO \( (\beta = -0.27, p = 0.01) \), and \( \dot{V}_{\text{O}_2} \) chemosensitivity \( (\beta = 0.49, p < 0.001) \) were independent determinants of \( \dot{V}_{\text{E}}/\dot{V}_{\text{CO}_2} \) 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 \( \dot{V}_{\text{O}_2} \) chemosensitivity increased significantly in the training group. The \( \dot{V}_{\text{E}}/\dot{V}_{\text{CO}_2} \) slope decreased marginally \( (p = 0.11) \). The changes in \( \dot{V}_{\text{E}}/\dot{V}_{\text{CO}_2} \) slope were correlated only with those in \( \dot{V}_{\text{O}_2} \) chemosensitivity \( (r = 0.50, p < 0.001) \).

Conclusion: After acute myocardial infarction, exercise hyperventilation is seen in association with aging, enhanced hypercapnic \( \dot{V}_{\text{E}}/\dot{V}_{\text{CO}_2} \) chemosensitivity, and reduced TlCO even in the absence of overt heart failure. The correlation of \( \dot{V}_{\text{E}}/\dot{V}_{\text{CO}_2} \) attenuation after training with the reduction in \( \dot{V}_{\text{O}_2} \) chemosensitivity suggests that exercise training may reduce increased \( \dot{V}_{\text{E}}/\dot{V}_{\text{CO}_2} \) slope, at least partially by reducing \( \dot{V}_{\text{O}_2} \) chemosensitivity.

Abbreviations: \( \text{FEV}_1 \), forced expiratory volume in one second; LVEF, left ventricular ejection fraction; TlCO, carbon monoxide transfer factor; VC, vital capacity; \( \dot{V}_{\text{E}}/\dot{V}_{\text{CO}_2} \), minute ventilation relative to carbon dioxide production; \( \dot{V}_{\text{O}_2} \), oxygen uptake.
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 VO₂ was determined as the averaged VO₂ 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 (VE/VTCO₂ 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 the standard nomograms incorporating age, sex, height, and weight. 21

**CO₂ chemosensitivity measurement**

According to the CO₂ rebreathing method reported by Read, "we measured CO₂ chemosensitivity as follows. Breath by breath minute ventilation and end tidal CO₂ concentration were measured by the gas analyzer 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

---

**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 based on our previous study.

**Table 1 Patient characteristics**

<table>
<thead>
<tr>
<th>Group</th>
<th>Group Tlow</th>
<th>Group Thigh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57 (13)</td>
<td>58 (11)</td>
</tr>
<tr>
<td>Men/women</td>
<td>7/3</td>
<td>22/5</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>46 (9)</td>
<td>45 (8)</td>
</tr>
<tr>
<td>Forrester’s subset II or greater</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Drug administration</td>
<td>ACE inhibitors</td>
<td>8 (80%)</td>
</tr>
<tr>
<td>β Blockers</td>
<td>4 (40%)</td>
<td>7 (30%)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Spirometry</td>
<td>VC (%predicted)</td>
<td>105 (13)</td>
</tr>
<tr>
<td>FEV₁ (%predicted)</td>
<td>82 (6)</td>
<td>86 (11)</td>
</tr>
<tr>
<td>TlCO (%predicted)</td>
<td>102 (17)</td>
<td>105 (17)</td>
</tr>
<tr>
<td>Peak VO₂ (mL/kg/min)</td>
<td>24 (5)</td>
<td>23 (5)</td>
</tr>
<tr>
<td>VE/VTCO₂ slope</td>
<td>30 (10)</td>
<td>25 (3)*</td>
</tr>
</tbody>
</table>

Data are mean (SD) or number of patients. *p<0.05 v control; Tp<0.05 v group Tlow (pretraining slope of minute ventilation relative to carbon dioxide production [VE/VTCO₂] <30).

**Exercise training programme**

Initial early sessions of the exercise training programme were conducted three to five times a week for 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 VO₂ was determined as the averaged VO₂ 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 (VE/VTCO₂ 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 the standard nomograms incorporating age, sex, height, and weight. 21

**CO₂ chemosensitivity measurement**

According to the CO₂ rebreathing method reported by Read, "we measured CO₂ chemosensitivity as follows. Breath by breath minute ventilation and end tidal CO₂ concentration were measured by the gas analyzer 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
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 $\frac{VE}{VCO_2}$ slope and spirometric parameters in 60 patients under the baseline conditions. Three pulmonary function variables were all weakly but significantly correlated with the $\frac{VE}{VCO_2}$ slope during exercise (percentage of predicted normal carbon monoxide transfer factor $\%TTCO$, $r = -0.33$, $p = 0.01$; percentage of predicted normal vital capacity $\%VC$, $r = -0.28$, $p = 0.03$; and percentage of predicted forced expiratory volume in one second $\%FEV_1$, $r = -0.30$, $p = 0.02$). CO$_2$ chemosensitivity was relatively strongly correlated with the $\frac{VE}{VCO_2}$ slope ($r = 0.62$, $p < 0.001$).

**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 $V_O_2$ (table 1). However, when the three groups were compared separately (groups $T_{high}$, $T_{low}$, and C), peak $V_O_2$ in group $T_{high}$ was significantly lower than that in group $T_{low}$ 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 $\frac{VE}{VCO_2}$ slope**

In the 60 patients under the baseline conditions, three pulmonary function variables were all weakly but significantly correlated with the $\frac{VE}{VCO_2}$ slope during exercise ($\%TTCO$, $r = -0.33$, $p = 0.01$; $\%VC$, $r = -0.28$, $p = 0.03$; $\%FEV_1$, $r = -0.30$, $p = 0.02$) (fig 1), while CO$_2$ chemosensitivity was relatively strongly correlated with the $\frac{VE}{VCO_2}$ slope ($r = 0.62$, $p < 0.001$).

![Figure 1](http://www.heartjnl.com) Relation between the slope of minute ventilation relative to carbon dioxide production ($\frac{VE}{VCO_2}$) and CO$_2$ chemosensitivity, and relations between the $\frac{VE}{VCO_2}$ slope and spirometric parameters in 60 patients under the baseline conditions. Three pulmonary function variables were all weakly but significantly correlated with the $\frac{VE}{VCO_2}$ slope during exercise (percentage of predicted normal carbon monoxide transfer factor $\%TTCO$, $r = -0.33$, $p = 0.01$; percentage of predicted normal vital capacity $\%VC$, $r = -0.28$, $p = 0.03$; and percentage of predicted forced expiratory volume in one second $\%FEV_1$, $r = -0.30$, $p = 0.02$). CO$_2$ chemosensitivity was relatively strongly correlated with the $\frac{VE}{VCO_2}$ slope ($r = 0.62$, $p < 0.001$).
phase haemodynamic impairment (subset II or greater of For- rester 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 (β = 0.49, p < 0.0001) compared with age (β = 0.29, p = 0.007) and %TLCO (β = −0.27, p = 0.008). These results suggest that CO₂ chemosensitivity has an important role in determining the VE/VCO₂ slope early after acute myocardial infarction, although multiple factors seem to be involved in the pathogenesis.

Changes in peak VO₂ and VE/VCO₂ slope

Peak VO₂ and VE/VCO₂ 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 VO₂ 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 VE/VCO₂ 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 VE/VCO₂ 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) l/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

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

<table>
<thead>
<tr>
<th></th>
<th>Group C</th>
<th>Group T_low</th>
<th>Group T_high</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>Exercise testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak VO₂ (ml/kg/min)</td>
<td>24 (5)</td>
<td>25 (6)</td>
<td>23 (5)</td>
</tr>
<tr>
<td>VE/VCO₂ slope</td>
<td>30 (10)</td>
<td>29 (8)</td>
<td>25 (3)</td>
</tr>
<tr>
<td>CO₂ chemosensitivity</td>
<td>1.3 (1.0)</td>
<td>1.4 (1.3)</td>
<td>1.3 (0.5)</td>
</tr>
<tr>
<td>Spirometry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VC (%predicted)</td>
<td>105 (13)</td>
<td>107 (18)</td>
<td>102 (12)</td>
</tr>
<tr>
<td>FEV₁ (%predicted)</td>
<td>82 (6)</td>
<td>81 (7)</td>
<td>86 (11)</td>
</tr>
<tr>
<td>TCO₂ (%predicted)</td>
<td>102 (17)</td>
<td>108 (17)</td>
<td>105 (17)</td>
</tr>
</tbody>
</table>

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

Figure 2: Relation between changes (Δ) in the VE/VCO₂ slope and in CO₂ chemosensitivity, and between changes in the VE/VCO₂ slope and in spirometric parameters in the training group (n = 50). Changes in the VE/VCO₂ 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.
group. This attenuation was significant in both subgroups (p < 0.001 for group TLow, p < 0.001 for group THigh).

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 THigh (p < 0.05) and in %TLCO only in group TLow (p < 0.001). None of these three parameters was significantly different in group C.

Changes in VE/VCO2 slope versus changes in CO2 chemosensitivity and pulmonary function parameters

In the 50 patients in the training group, the changes from baseline in the VE/VCO2 slope after three months were significantly correlated with changes in CO2 chemosensitivity (r = 0.50, p < 0.001). No such significant correlation was found for any of the three pulmonary function variables (fig 2). When analysed separately within each subgroup, significant changes were observed in %VC only in group THigh (p < 0.05) and in %TLCO only in group TLow (p < 0.001). None of these three parameters was significantly different in group C.

DISCUSSION

Our previous study showed that an increased VE/VCO2 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. 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 TLow with increased VE/VCO2 relative to baseline had higher than normal CO2 chemosensitivity. (2) Age, TLCO, and CO2 chemosensitivity were independently related to the baseline VE/VCO2 slope. (3) Regardless of the baseline level, CO2 chemosensitivity was significantly attenuated after exercise training. Changes in the VE/VCO2 slope after exercise training were not significantly correlated only with changes in CO2 chemosensitivity, not with any of the other parameters. These results suggest that, even in the absence of overt heart failure, VE/VCO2 slope is increased in a significant proportion of postinfarct patients in association with aging, reduced TLCO, and enhanced CO2 chemosensitivity, and that the increased VE/VCO2 slope may be reduced by exercise training, at least partially, through the attenuation of CO2 chemosensitivity. To our knowledge, in patients with heart disease, the possible role of CO2 chemosensitivity in the improvement in increased VE/VCO2 slope after exercise training has not been shown elsewhere.

Mechanisms for increased VE/VCO2 slope

Although the detailed mechanisms underlying the increased VE/VCO2 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. However, a normal or near normal VE/VCO2 slope is not uncommon in patients with the most severe left ventricular dysfunction, such as candidates for cardiac transplantation. Conversely, the VE/VCO2 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 VE/VCO2 slope in previous studies examining patients with severe heart failure. 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 activity 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 VE/VCO2 slope.

The present study has shown that, in patients after acute myocardial infarction, the VE/VCO2 slope increases in association with aging, decreased TLCO, and enhanced CO2 chemosensitivity. Among these three factors, enhanced CO2 chemosensitivity seems to be the most potent determinant. The increase in VE/VCO2 slope with aging was reported in healthy subjects. Reduction of TLCO is well known in chronic heart failure. In the study by Guazzi and colleagues 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 VE/VCO2 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 VE/VCO2 slope in our patients; however, changes in TLCO after three months were not associated with changes in the VE/VCO2 slope.
In our patients, the VE/VCO₂ slope was relatively strongly correlated with peak V\text{O₂}, similar to reports from studies in patients with heart failure. A weak but significant correlation between VE/VCO₂ 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.

**VE/VCO₂ slope in patients with acute myocardial infarction**

Although, as described above, several factors should contribute to the increased VE/VCO₂ 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 VE/VCO₂ slope. These patients are known to have heightened sympathetic tone, which is reported to increase ventilation, 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 VE/VCO₂ slope, one can suppose that some manipulations to reduce CO₂ chemosensitivity would improve the VE/VCO₂ slope, leading to an amelioration of breathlessness during exercise. A study by Chua and colleagues 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 VE/VCO₂ slope and an improvement in exercise tolerance (peak V\text{O₂}) and sensation of dyspnoea at a given work rate. On the other hand, it is well established that chronic physical training attenuates increased VE/VCO₂ slope in patients with chronic heart failure, whereas the VE/VCO₂ slope is shown to remain unchanged in normal subjects, suggesting that the VE/VCO₂ slope may be altered only when the baseline level is increased. These findings are in agreement with our results—that is, the VE/VCO₂ slope was attenuated only in group \( T_{high} \) with the increased baseline level of VE/VCO₂ slope.

Our finding that changes in the VE/VCO₂ 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, 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 \( T_{high} \) 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. Chemosensitivity is known to be lower in the elderly than in the younger subjects 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 VE/VCO₂ 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.

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 V\text{O₂} 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 VE/VCO₂ 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 VE/VCO₂ 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.

ACKNOWLEDGEMENTS

This study was supported by Research Grants for Cardiovascular Diseases (11C-7) from the Ministry of Health and Welfare of Japan, by a Grant-in-Aid for Scientific Research (C-11670730) from the Japan Society for the Promotion of Science, and by the Program for Promotion of Fundamental Studies in Health Science from the Organization for Pharmaceutical Safety and Research.

REFERENCES

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

T Tomita, H Takaki, Y Hara, F Sakamaki, T Satoh, S Takagi, Y Yasumura, N Aihara, Y Goto and K Sunagawa

Heart 2003 89: 404-410
doi: 10.1136/heart.89.4.404

Updated information and services can be found at:
http://heart.bmj.com/content/89/4/404

These include:

References
This article cites 38 articles, 15 of which you can access for free at:
http://heart.bmj.com/content/89/4/404#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

Drugs: cardiovascular system (8842)
Acute coronary syndromes (2742)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/