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 (VE/VCO₂) 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 CO₂ 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, CO₂ 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 VE/VCO₂ slope. Multivariate regression analysis showed that age (β = 0.29, p = 0.01), %Tlco (β = –0.27, p = 0.01), and CO₂ chemosensitivity (β = 0.49, p < 0.001) were independent determinants of VE/VCO₂ 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 CO₂ chemosensitivity increased significantly in the training group. The VE/VCO₂ slope decreased marginally (p = 0.11). The changes in VE/VCO₂ slope were correlated only with those in CO₂ chemosensitivity (r = 0.50, p < 0.001).

Conclusion: After acute myocardial infarction, exercise hyperventilation is seen in association with aging, enhanced hypercapnic CO₂ chemosensitivity, and reduced Tlco, even in the absence of overt heart failure. The correlation of VE/VCO₂ attenuation after training with the reduction in CO₂ chemosensitivity suggests that exercise training may reduce increased VE/VCO₂ slope, at least partially by reducing CO₂ 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 (CO₂) production (VE/VCO₂ slope), which is known to be related to the severity of heart disease. Furthermore, this index has recently received increased attention since it is a powerful prognostic marker independent of peak oxygen uptake (VO₂) and left ventricular function. Several factors such as inefficient ventilation (perfusion–ventilation mismatch, rapid–shallow respiratory pattern), alteration in CO₂ chemosensitivity, ergoreflex overactivation, and possibly reduced alveolar–capillary membrane diffusing capacity (carbon monoxide transfer factor (Tlco)) 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. 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. We also have recently reported that, even in the absence of overt heart failure, some patients with acute myocardial infarction exhibited an increased VE/VCO₂ slope, which was attenuated after an exercise training programme. 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 CO₂ 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.

We therefore measured exercise ventilation, hypercapnic CO₂ 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 VE/VCO₂ 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 CO₂ chemosensitivity contributes to the attenuation of the VE/VCO₂ 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; VE/VCO₂, minute ventilation relative to carbon dioxide production; VO₂, oxygen uptake
**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 Forrester’s subset II or greater according to the CO2 rebreathing method reported by Read.24 We measured CO2 chemosensitivity as follows. Breath by breath measurements of the forced expiratory volume in one second (peak V~E~), peak oxygen uptake (peak VO~2~), minute ventilation (VE), and respiratory compensation point was used as the index of the ventilatory response to exercise (VE/V~CO2~ slope).25

**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 were not altered throughout 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 VO~2~ was determined as the averaged VO~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 (VE/V~CO2~ slope).25

**CO2 chemosensitivity measurement**

According to the CO2 rebreathing method reported by Read,24 we measured CO2 chemosensitivity as follows. Breath by breath measurements of 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 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 exceeded 10%. CO2 chemosensitivity was defined as the slope of the increase in minute ventilation relative to the increase in end tidal CO2 concentration exceeded 10%. CO2 chemosensitivity was expressed in terms of l/min/mm Hg. Because CO2 chemosensitivity reported by others varies considerably,26–28 we examined age matched healthy subjects (n = 9, 62 (8 years old) without any cardiovascular disease.

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**Table 1 Patient characteristics**

<table>
<thead>
<tr>
<th>Group</th>
<th>Group T<del>pre</del></th>
<th>Group T<del>high</del></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>
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Drugs: ACE inhibitors 8 (80%); β blockers 4 (40%); Digoxin 0 (0%).

Spirometry: VC (%predicted) 105 (13); FEV1 (%predicted) 82 (6); TCO (liter per second) 102 (17). Peak VO2 (ml/kg/min) 24 (5); VE/V~CO2~ slope 30 (10). Data are mean (SD) or number of patients. *p<0.05 v control, Tp<0.05 v group T~pre~.
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 VE/VCO₂ slope and spirometric parameters in 60 patients under the baseline conditions. Three pulmonary function variables were all weakly but significantly correlated with the VE/VCO₂ 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 [%FEV₁], \( r = -0.30, p = 0.02 \)). CO₂ chemosensitivity was relatively strongly correlated with the VE/VCO₂ slope (\( r = 0.62, p < 0.001 \)).

RESULTS
At baseline, there was no significant difference between the training group (groups T₃₄₀₀ and T₃₈₀₀) 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 VO₂ (table 1). However, when the three groups were compared separately (groups T₃₄₀₀, T₃₈₀₀, and C), peak VO₂ in group T₃₄₀₀ was significantly lower than that in group T₃₈₀₀ 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 T₃₄₀₀ but these differences did not reach significance.

In nine age matched normal healthy subjects, hypercapnic CO₂ 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 T₃₈₀₀ (1.3 (0.5) l/min/mm Hg) under baseline conditions (at entry into the exercise training programme). Only group T₃₈₀₀ (2.0 (0.7) l/min/mm Hg) had higher than normal values of CO₂ chemosensitivity (\( p < 0.05 \)).

Baseline relation of variables of pulmonary function and CO₂ chemosensitivity to VE/VCO₂ slope
In the 60 patients under the baseline conditions, three pulmonary function variables were all weakly but significantly correlated with the VE/VCO₂ slope during exercise (%TLCO, \( r = -0.33, p = 0.01 \); %VC, \( r = -0.28, p = 0.03 \); %FEV₁, \( r = -0.30, p = 0.02 \)) (fig 1), while CO₂ chemosensitivity was relatively strongly correlated with the VE/VCO₂ slope (\( r = 0.62, p < 0.001 \)).
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 $V^\sim\text{E}/V^\sim\text{CO2}$ slope early after acute myocardial infarction, although multiple factors seem to be involved in the pathogenesis.

Changes in peak V\text{o2} and $V^\sim\text{E}/V^\sim\text{CO2}$ slope

Peak V\text{o2} and $V^\sim\text{E}/V^\sim\text{CO2}$ 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 V\text{o2} 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\text{low}, $p < 0.001$ for group T\text{high}). The $V^\sim\text{E}/V^\sim\text{CO2}$ slope was significantly attenuated in group T\text{high} ($p < 0.001$) but not in group T\text{low} after three months compared with the baseline value. The changes in $V^\sim\text{E}/V^\sim\text{CO2}$ 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

![Figure 2](http://heart.bmj.com/)
group. This attenuation was significant in both subgroups (p < 0.001 for group T_high, p < 0.001 for group T_low).

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 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, the changes in the VE/Vco2 slope were significantly correlated with changes in CO2 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 CO2 chemosensitivity may have a central role in improving the exercise hyperventilation (that is, increased VE/Vco2 slope) seen in patients after acute myocardial infarction.

**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 T_high 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 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.31 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 failure 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.
CO₂ chemosensitivity after exercise training

In our patients, the V̇E/V̇CO₂ slope was relatively strongly correlated with peak V̇O₂, similar to reports from studies in patients with heart failure. A weak but significant correlation between V̇E/V̇CO₂ 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/V̇CO₂ slope in patients with acute myocardial infarction**

Although, as described above, several factors should contribute to the increased V̇E/V̇CO₂ 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 V̇E/V̇CO₂ 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 V̇E/V̇CO₂ slope, one can suppose that some manipulations to reduce CO₂ chemosensitivity would improve the V̇E/V̇CO₂ slope, leading to an amelioration of breathlessness during exercise. A study by Chu 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 V̇E/V̇CO₂ slope and an improvement in exercise tolerance (peak V̇O₂) and sensation of dyspnoea at a given work rate. On the other hand, it is well established that chronic physical training attenuates increased V̇E/V̇CO₂ slope in patients with chronic heart failure, whereas the V̇E/V̇CO₂ slope is shown to remain unchanged in normal subjects, suggesting that the V̇E/V̇CO₂ slope may be altered only when the baseline level is increased. These findings are in agreement with our results—that is, the V̇E/V̇CO₂ slope was attenuated only in group T₃months with the increased baseline level of V̇E/V̇CO₂ slope.

Our finding that changes in the V̇E/V̇CO₂ 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 T₃months were comparable with the mean value measured in healthy subjects. Only group T₃months 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 V̇E/V̇CO₂ 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 T₃months, which trended towards a lower LVEF and a significantly reduced peak V̇O₂ 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 V̇E/V̇CO₂ slope during exercise occurs in association with aging, reduced T₃months, 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 V̇E/V̇CO₂ 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.

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