Correspondence

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Attenuation of Unfavorable Sympathetic Hyperactivity Induced by Long-Term Physical Training in Postinfarction Patients: Fact or Speculation?

To the Editor:

Recently, Giannuzzi et al1 eloquently described the beneficial effect of long-term exercise training on left ventricular remodeling in postinfarction patients. An earlier report from Coats et al2 demonstrated that training can improve autonomic function (mainly in terms of RR variability and norepinephrine spillover) in patients with chronic heart failure but failed to show significant changes in resting catecholamine levels after a short-term exercise program. In an attempt to explain their findings, Giannuzzi et al used a series of reports describing the reduction of catecholamine levels by exercise training in subjects with normal left ventricular function3,4 and speculated that this effect exists in patients with left ventricular dysfunction as well. However, this phenomenon is no longer conjectural because it has been demonstrated clearly in postinfarction patients with severe left ventricular dysfunction after long-term exercise rehabilitation. Moreover, that study also showed a beneficial effect of the rehabilitation program on atrial natriuretic peptide. We hope that clarification of these points will provide additional support for the findings of Giannuzzi and his team.

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Response

We greatly appreciate the letter of Drs Tenenbaum and Shemesh, who give us the opportunity to provide additional comments concerning the role of exercise training in the remodeling process among postinfarction patients with left ventricular dysfunction and the long-term effect of physical training on the autonomic balance and neurohormonal activation.

After the initial conflicting results, an increasing body of evidence has now demonstrated clearly that patients with poor left ventricular function after an uncomplicated myocardial infarction may benefit from regular exercise training without any additional deterioration of ventricular volumes and function.2,5 More importantly, we recently documented in a large group of postinfarction patients with left ventricular dysfunction that long-term exercise training may attenuate the unfavorable remodeling process and even improve both regional and global function over time. We6 also reported similar results in preliminary form in patients with chronic heart failure, in whom training actually lessened left ventricular dilatation and dysfunction.

Exercise training has been shown to increase functional work capacity and at the same time to reduce catecholamine levels and vascular peripheral resistances and enhance heart rate variability and baroreflex gain, both in subjects with normal ventricular function as well as in patients with left ventricular dysfunction and heart failure. Shemesh et al briefly reported significantly lower levels of resting norepinephrine and atrial natriuretic peptide in postinfarction patients with reduced ejection fraction who were undergoing long-term cardiac rehabilitation. This result and previous observations strongly indicate a lower sympathetic activity after training. The real point of speculation in our article was not the existence of this effect but the possible interplay of this factor with others, including improvement in myocardial blood flow.

Although we did not assess neurohormonal changes, the features of the training response we found in our study are consistent with the usual response to regular exercise, including reduction in resting heart rate and blood pressure and in exercise heart rate and rate-pressure product.2 Indexes of heart rate variability also improved after training, particularly in patients with an initial autonomic derangement as expressed by a reduced heart rate variability.2 These findings reflect beneficial changes in autonomic balance and/or baroreflex gain and are in agreement with the attenuation of the vasoconstrictor influences, mainly due to sympathetic hyperactivity, and the increased vagal tone described after training. The beneficial changes in autonomic balance induced by physical training may actually limit the deleterious effects of sympathetic hyperactivity on left ventricular remodeling and function.

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Lung Function and Exercise Gas Exchange in Chronic Heart Failure

To the Editor:

This letter follows the report from a multicenter study of exercise ventilatory and gas exchange responses in 130 patients with heart failure (HF).

Average exercise PaO2 and PAO2 were observed to be normal in spite of a relatively high VD/VT, which was compensated for by a marked hyperventilation (VE/V˙O2 close to 40 even at comparatively low workloads). The authors thus suggest that patients with HF present a condition of reduced perfusion in a well-ventilated lung with no disturbance in gas exchange. The mean P(A−a)O2 was indeed found to be normal at ≈20 mm Hg. However, PaO2, P(A−a)O2, and, to a lesser extent, PAO2 were widely dispersed around average values. In a large number of patients, supranormal values, seldom observed in clinical practice, were observed for PAO2 (>110 mm Hg in ≈30 patients), PAO2 (>130 mm Hg in ≈15 patients), and P(A−a)O2 (<10 mm Hg in ≈30 patients). These values at the upper range of the distributions correctly fit the description of a "reduced perfusion in a well-ventilated lung." In contrast, at the lower range of the distribution, ≈30 patients exhibited P(A−a)O2 values >30 mm Hg, and this was independent of the achieved peak VO2. It should be remembered that in 77 subjects with normal lung function and gas exchange, Hansen et al2 observed exercise P(A−a)O2 >35 mm Hg in only 3. We thus believe that the simple and attractive "high VA/Q" model due to a high VD/VT proposed to explain the exaggerated ventilatory response in patients with HF only fits a limited number of these patients, namely, those with normal or supranormal P(A−a)O2 values. However, the large prevalence of a wide exercise P(A−a)O2 in these patients suggests that additional factors can contribute to the marked hyperventilation observed, such as ventilation-perfusion mismatch due to poor alveolar ventilation and/or diffusion limitation. These and other possible disturbances in lung function and gas exchange in patients with HF should not be overlooked in clinical practice.

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Response

In response to the letter of Aguilaniu and colleagues, we must point out that their letter incorrectly describes our findings. They state that we “suggest that patients with HF” have “no disturbance in gas exchange.” We did find a disturbance in gas exchange in our patients with chronic HF, the nature of which was the primary message of our article. We found that the dead space/tidal volume ratio (VD/VT) and arterial–end tidal Pco2 difference [P(a−ET)CO2] increased systematically as peak exercise performance decreased. These findings indicate that high ventilation-perfusion (VA/Q) ratio lung units developed as exercise tolerance worsened, findings expected with regional reduction in pulmonary blood flow relative to ventilation. In contrast, the average arterial Po2 (PAO2) and alveolar–arterial Po2 difference [P(A−a)O2] values remained normal at peak exercise and were uninfluenced by the severity of the exercise. These observations suggest that there is no systematic development of low VA/Q lung units as exercise tolerance worsens.

The letter of Aguilaniu et al has as its main concern the values of PaO2 and P(A−a)O2 in our HF patients. They used the study of Hansen et al2 as the reference for normal values (adult men with average age of 54 years). These values in our HF population have a greater dispersion than reported by Hansen et al2 (PaO2=98.1±15.3 versus 100.6±9.9 for the HF and normal populations, respectively, and P(A−a)O2=20.5±13.7 versus 19.0±8.8 for the HF and normal populations, respectively, mean±SD). These values are not significantly different. Nine of our 83 patients had a PaO2 value ranging from 61 to 79 at peak exercise, values that we regard to be abnormal. However, these low values were not systematically related to the extent of exercise limitation. Aguilaniu et al state that a PaO2 of >110 at maximal exercise is seldom seen in clinical practice at peak exercise. I am not sure of the altitude of the laboratory at which Dr Aguilaniu et al work (critically important), but at sea level, these values, while not usual, are not uncommon at peak exercise. Given the data of Hansen et al,2 10 (13.5%) of 74 normal subjects had a PaO2 value >110 at peak exercise compared with 17 (20.5%) of 83 in our HF population. The high values at peak exercise could be accounted for by a combination of hyper-ventilation and high respiratory exchange ratio (RER). Thus, the alveolar Po2 will become 130 when Paco2=27 and RER=1.5 (only 3 of our 83 patients had PaO2 values in the range of 130).

The increased dispersion in our HF population might have been due to chronic changes resulting from repeated episodes of pulmonary edema or the ravages of chronic cigarette smoking. We did not prescreen our HF patients for subtle pulmonary disease, as was done by Hansen et al.2 We also cannot exclude the possibility that random technical errors might have occurred in this multicenter study to account for the increased dispersion of our data compared with that reported by Hansen et al.2

The major finding described in our report is that patients with chronic HF have unique lung pathophysiology. They develop high VA/Q ratio lung units as exercise capacity worsens, without development of low VA/Q ratio lung units. This impairment-related abnormality in lung function, along with the increased VCO2 relative to VO2 that our study...
describes, may account for the high frequency of dyspnea reported by HF patients.

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Hepatitis C Virus Infection and Chronic Active Myocarditis

To the Editor:

Okabe et al.1 studied the association of hepatitis C virus (HCV) infection with chronic active myocarditis, a variant form of chronic myocarditis characterized by numerous lymphocytic clusters and myocardial cell damage, in 3 patients. Using the so-called genomic analysis to detect positive (genomic) and negative (repetitive) strands of HCV RNA, the authors found that all 3 patients had both positive- and negative-strand HCV RNA in their myocardial tissue. They therefore concluded that HCV can replicate in inflamed myocardial tissue and may contribute to the development of chronic active myocarditis. Although their findings are interesting and the association of HCV infection with chronic active myocarditis may be true, controversial issues still exist that should be carefully addressed before drawing a final conclusion.

First, the strand-specific polymerase chain reaction (PCR) used by the authors to detect positive- and negative-strand HCV RNA may not be stringent enough, and possible false positivity cannot be excluded. Previous studies2,3 have questioned the strand specificity of HCV sequences detected in cell samples by heat inactivation of reverse transcriptase alone. Because cDNA can still be synthesized in the presence of Taq polymerase (reverse transcription activity in vitro), this may lead to false-positive results. Accordingly, we and other investigators have treated samples with RNase after heat inactivation to eliminate both positive and negative strands of RNA to further minimize the possible false positivity.2,4 Second, HCV infection of lymphocytic cells in patients with chronic hepatitis C has been documented.5,6 Thus, the HCV sequences detected in the myocardial tissue of patients with chronic active myocarditis could be derived from the infiltrating lymphocytes actively infected by HCV and not from the myocardial cells themselves.

Accordingly, the suggestion by Okabe and colleagues that HCV not only has a tropism to myocardial cells but also can replicate in them and may play a role in the development of an unusual form of myocarditis should be interpreted cautiously because of the limited case numbers studied and the possible false positivity in detecting negative strands of HCV RNA. Further larger studies that include adequate tissue samples and more convincing methods, such as localization of HCV antigens and/or HCV genome, are needed to confirm whether HCV is one of the responsible agents.

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Response

We appreciate the comments of Drs Kao and Hwang regarding the reverse-transcription polymerase chain reaction (RT-PCR) we used for genomic analysis of hepatitis C virus (HCV)1 in 3 patients with chronic active myocarditis.

We agree that heat denaturation after RT incubation is insufficient to prevent self-transcription of both the positive and negative strands of HCV RNA.2 To minimize the possibility of self-anneling of HCV sequences, we adopted a relatively high reverse transcription PCR. J Virol. 1995;69:8079–8083.

In our article,1 further evidence must be obtained by a more convincing method, such as in situ hybridization.

In our study,1 HCV sequences may have been derived from lymphocytes infiltrating the myocardium, as mentioned by Drs Kao and Hwang. However, this possibility does not deny a relationship between HCV infection and chronic active myocarditis, because these lymphocytes appear to play a major role in triggering and/or maintaining myocarditic activity. As discussed in our article,1 further evidence must be obtained by a more convincing technique, such as in situ hybridization.

We believe that HCV infection contributes to the eventual development of a failing dilated heart but assume that this situation may be rare. We recently reviewed the clinical charts of patients who were admitted to Fukuoka University Hospital for invasive cardiac evaluation. In 31 consecutive patients (including
21 men, mean age 45.1 ± 13.9 years) with dilated cardiomyopathy (DCM) who were admitted from January 1993 to September 1997, HCV antibody was detected in 3 cases (9.7%). In 246 consecutive patients (including 150 men, mean age 63.4 ± 12.9 years) with ischemic heart disease (IHD) who were admitted from May 1996 to September 1997, HCV antibody was present in 13 cases (5.5%). These IHD patients had no previous major surgery, including a cardiac operation, and none of them was on maintenance hemodialysis. The incidence of HCV antibody did not differ significantly between the DCM and IHD patients (Fisher’s exact test). This is inconsistent with a recent report by Matsumori et al.4

We agree that a large-scale study is needed to confirm the relationship between HCV infection and a failing heart (ie, DCM).

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Prediction of Transition to Chronic Atrial Fibrillation in Patients With Paroxysmal Atrial Fibrillation

To the Editor:

We read with great interest the recent report of Abe et al1 demonstrating that P-wave–triggered signal-averaged electrocardiography may be useful to predict the transition to chronic atrial fibrillation in patients with paroxysmal atrial fibrillation. In their study, although sex, age, and presence of organic heart disease were not associated with an increased risk for the transition to chronic atrial fibrillation, patients with the abnormality of a P-wave–triggered signal-averaged ECG had an 11-fold greater risk for chronic atrial fibrillation than those without the abnormality. Echocardiographically, left atrial dimension in patients with chronic atrial fibrillation was larger than that in patients with paroxysmal atrial fibrillation (40.5 versus 36.4 mm, P < 0.05), but there were no significant differences in left ventricular dimensions measured at end diastole and end systole or in ejection fraction between the 2 groups.

In contrast to the findings by Abe et al., we2 previously reported that congestive heart failure and reduction in left ventricular ejection fraction were predictors of the transition to chronic atrial fibrillation in patients with new-onset atrial fibrillation. To identify predictors of the transition to chronic atrial fibrillation within the first year after onset, we retrospectively reviewed clinical records, standard 12-lead ECGs, and M-mode echocardiograms of 137 patients with new-onset, nonparoxysmal atrial fibrillation. One year after onset, 30 (22%) of 137 patients showed a transition to chronic atrial fibrillation, and the other 107 continued to have paroxysmal atrial fibrillation. Compared with patients with paroxysmal atrial fibrillation, patients with chronic atrial fibrillation were older at the time of onset (70.1 versus 62.4 years, P < 0.01), more frequently had diabetes mellitus (37% versus 19%, P < 0.05), and more frequently had congestive heart failure (13% versus 3%, P < 0.05). These patients also had higher cardiothoracic ratios on chest x-ray (52.0% versus 47.0%, P < 0.01), greater f-wave amplitude in lead V1 on ECG (1.48 versus 1.06 mm, P < 0.05), larger left atrial dimension measured by echocardiography (41.0 versus 34.2 mm, P < 0.01), larger left ventricular end-systolic dimension (32.9 versus 29.7 mm, P < 0.05), and lower ejection fraction (0.71 versus 0.76, P < 0.05). Furthermore, the presence of any 1 of the following 7 factors was associated with an increased risk for the transition to chronic atrial fibrillation: age > 65 years (32% versus 11%, P < 0.01), diabetes mellitus (35% versus 18%, P < 0.05), congestive heart failure (57% versus 20%, P < 0.05), cardiothoracic ratio > 50% (41% versus 11%, P < 0.01), f-wave amplitude in lead V1 > 2.0 mm (80% versus 20%, P < 0.01), left atrial dimension > 38 mm (34% versus 5%, P < 0.01), and ejection fraction < 0.76 (35% versus 4%, P < 0.01). When each of these 7 significant predictors was assigned 1 point in risk score, the transition to chronic atrial fibrillation occurred in > 88% of the patients with a risk score > 4 (a high-risk group), in 22% of the patients with a risk score of 3 (an intermediate-risk group), and in < 6% of the patients with a risk score < 2 (a low-risk group).

The discrepancy between these 2 studies may be due to patient characteristics. Patients in the study by Abe et al were outpatients who had maintained cardiac function relatively well, whereas our study patients were recruited in part from an inpatient population with more congestive heart failure or moderate to severe cardiac dysfunction. This suggests that P-wave–triggered signal-averaged electrocardiography is useful to predict the transition to chronic atrial fibrillation, especially in patients with normal cardiac function. On the other hand, in the population including patients with impaired cardiac function, we propose that congestive heart failure and reduced left ventricular ejection fraction are important predictors of the transition to chronic atrial fibrillation. Furthermore, the major advantage of our proposed predictors and risk scoring system is that they allow physicians to identify patients with new-onset atrial fibrillation at high risk for the transition to chronic atrial fibrillation using routinely available clinical parameters.

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Response

We appreciate the interest shown by Dr Sakamoto and his colleagues in our article1 and their valuable comments using their results. They raised some important issues on prediction of transition to chronic atrial fibrillation. They proposed their
risk-scoring system using 7 predictors from clinical parameters, including indexes of heart failure, which proved to be significant in their retrospective study.\(^2\)

As they pointed out, the discrepancy between their and our results may be derived mainly from the difference of study population; study design (prospective or retrospective) may be also involved. Unfortunately, we have not yet conducted studies on the usefulness of P-wave signal–averaged electrocardiography for prediction of transition in patients with reduced cardiac function. However, we recently found that filtered P-wave duration prolongation can be a direct predictor of hospitalization for worsening heart failure in a prospective heart failure study\(^3\), in which Kaplan-Meier analysis revealed that patients with heart failure (ejection fraction <40\%) who had an abnormally prolonged filtered P wave (≥145 ms) were more often (29\% versus 4\%, log-rank test \(P<0.05\)) hospitalized for worsening heart failure than those without it during the follow-up period of 1 to 37 months. In addition, atrial fibrillation was often observed on admission. This implies that filtered P-wave duration may be an early predictor of heart failure deterioration as well as the establishment of atrial fibrillation. It is also well known that atrial fibrillation itself causes a deterioration in cardiac function, probably due to the disappearance of atrial contraction and shortening of the diastolic phase, although heart failure itself enhances the accomplishment of atrial fibrillation. Consequently, the mechanism for establishment of atrial fibrillation may be complicated in heart failure patients, in whom changes in autonomic nerve system, electrolytes, humoral factors, and hemodynamics often occur. In general, most clinical parameters are redundant and depend in part on each other. That is why the analysis had to be complex, especially in a prospective study. Subsequently, to make it simpler, we investigated only filtered P-wave characteristics, such as electrophysiological arrhythmogenic substrate, in patients without heart failure. Although the left atrial dimension and the number of atrial premature contractions a day were weakly but significantly different between the 2 groups with and without the transition in our study, we think that this might be because they were closely related to the filtered P-wave duration.

Many people would like to know what type of paroxysmal atrial fibrillation will eventually change to the chronic form because the prognosis and incidence of thromboembolism are different. Thus, we would like to propose again that P wave signal–averaged electrocardiography be used in patients without heart failure. If additional criteria in P-wave signal–averaged electrocardiography for patients with heart failure are proposed, our method will be more applicable in clinics.

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Attenuation of Unfavorable Sympathetic Hyperactivity Induced by Long-Term Physical Training in Postinfarction Patients: Fact or Speculation?
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Circulation. 1998;98:1042-1043
doi: 10.1161/01.CIR.98.10.1042

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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