Exercise-Induced Increase in Baroreflex Sensitivity Predicts Improved Prognosis After Myocardial Infarction

Maria Teresa La Rovere, MD; Chiara Bersano, MD; Marco Gnemmi, MD; Giuseppe Specchia, MD; Peter J. Schwartz, MD

Background—Despite the rational expectation for a survival benefit produced by exercise training among post–myocardial infarction (MI) patients, direct evidence remains elusive. Clinically, changes in autonomic balance toward lower vagal activity have consistently been associated with increased mortality risk; conversely, among both control and post-MI dogs, exercise training improved vagal reflexes and prevented sudden death. Accordingly, we tested the hypothesis that exercise training, if accompanied by a shift toward increased vagal activity of an autonomic marker such as baroreflex sensitivity (BRS), could reduce mortality in post-MI patients.

Methods and Results—Ninety-five consecutive male patients surviving a first uncomplicated MI were randomly assigned to a 4-week endurance training period or to no training. Age (51±8 versus 52±8 years), site of MI (anterior 41% versus 43%), left ventricular ejection fraction (52±13 versus 51±14%), and BRS (7.9±5.4 versus 7.9±3.4 ms/mm Hg) did not differ between the two groups. After 4 weeks, BRS improved by 26% (P=0.04) in trained patients, whereas it did not change in nontrained patients. During a 10-year follow-up, cardiac mortality among the 16 trained patients who had an exercise-induced increase in BRS ≥3 ms/mm Hg (responders) was strikingly lower compared with that of the trained patients without such a BRS increase (nonresponders) and that of the nontrained patients (0 of 16 versus 18 of 79 [23%], P=0.04). Cardiac mortality was also lower among responders irrespective of training (4% versus 24%, P=0.04).

Conclusions—Post-MI exercise training can favorably modify long-term survival, provided that it is associated with a clear shift of the autonomic balance toward an increase in vagal activity. (Circulation. 2002;106:945-949.)

Key Words: baroreceptors • death, sudden • exercise • myocardial infarction • nervous system, autonomic

Multiple studies have led to the rational suggestion that exercise training favorably influences cardiac mortality after a myocardial infarction (MI). For example, an AHA Task Force in 1987 recommended “the evaluation of exercise programs in selected groups of patients with ischemic heart disease at high risk for sudden death.” Eventually, all of these data stimulated the recommendation by the ACC/AHA practice guidelines that post-MI patients perform daily exercise. Nonetheless, direct evidence for a cause-effect relationship between exercise training and reduction in cardiac mortality among post-MI patients has remained disappointingly elusive over the years. This inconsistency was exemplified by the need to resort to a meta-analysis to provide the first evidence of benefit. The dishomogeneity of the populations under study, the coadministration of multiple interventions or behavioral changes, and especially the lack of a reliable physiological marker linking effective training and protection from lethal events may have compounded the problem.

In the early 1980s, we demonstrated that the post-MI risk for lethal arrhythmias was tightly associated with an autonomic alteration, characterized by reduced vagal or augmented sympathetic reflexes, as revealed by depressed baroreflex sensitivity (BRS). This experimental finding, destined to be confirmed years later at clinical level, paved the way to the concept that modulation of vagal activity would have made it possible to either increase or reduce the risk for cardiac and arrhythmic mortality. Among the diverse mechanisms capable of increasing cardiac vagal activity and reducing risk, exercise training appeared both effective and of immediate clinical applicability.

It was on this basis that in the mid-1980s we designed a prospective, randomized study aimed at testing the hypothesis that exercise training, at a “dose” sufficient to produce a quantifiably adequate increase in vagal reflexes, would have been associated with a long-term reduction in cardiac mortality among post-MI patients. In this study, we report the impact on survival, during a 10-year follow-up period, of producing an adequate increase in baroreflex sensitivity through exercise training.

Methods

The study population consisted of 95 consecutive male patients suffering from a first and recent MI, all admitted at the Centro...
Medico di Montescano in 1984 to 1985. After a symptom-limited exercise test (28±2 days after myocardial infarction), 24-hour Holter monitoring, and coronary angiography (31±3 days after the acute episode), patients were randomized to a 4-week training period or to a control group. The exercise sessions (30 minutes, 5 times a week) consisted of calisthenics and stationary bicycle ergometry. During the first week, the intensity of bicycle ergometry was adjusted to 75% of the heart rate at peak oxygen consumption measured during the pretraining exercise stress test. Thereafter, the amount of physical activity was increased to 85% during the second and third week and to 95% during the last week. All patients attended sessions, held by a cardiologist and a psychologist, dealing with secondary prevention of cardiovascular disease and stressing dietary changes and smoking cessation.

Exclusion criteria were atrial fibrillation or abnormal sinus node function, insulin-dependent diabetes, exercise-induced myocardial ischemia, and arterial blood pressure >160/90. All patients gave informed consent to participate in the study, which had been approved by the local ethical committee.

Baroreflex Sensitivity Assessment
Studies were carried out in the morning, after 30 minutes of supine rest. BRS was evaluated by administration of the vasoactive drug phenylephrine, as previously described. Briefly, heart rate and systolic arterial pressure (SAP) obtained directly from the radial or brachial artery were continuously recorded. Phenylephrine (2 to 3 μg/kg) was injected intravenously to raise systolic arterial pressure 15 to 30 mm Hg by at least 3 bolus injections separated by 10-minute intervals. The R-R intervals were plotted against the preceding arterial systolic peak, and a linear regression was performed for the points included between the beginning and the end of first significant increase in SAP. Regression lines with a statistically significant correlation coefficient ($P<0.05$) were accepted for analysis. BRS was assessed at entry and after 4 weeks both in trained and nontrained patients.

Follow-Up
Patients were followed at 3- to 4-month intervals from the time of entry into the study for the first 3 years. Thereafter, patients were contacted periodically by telephone to identify major clinical events and death. Out-of-hospital deaths were investigated by means of interview with the next of kin or patients' physicians or by the analysis of death certificates.

Statistical Analysis
Baseline characteristics of the study groups are presented as mean±SD. Because a BRS value <3 ms/mm Hg had been shown to identify an increased mortality risk, an increase of at least 3 ms/mm Hg was chosen as a priori to detect a clinically significant change in BRS (responders), whether induced by exercise training or time alone. Comparison between and within groups was performed by ANOVA. Categorical variables were compared by the $\chi^2$ test. Survival curves were estimated by the Kaplan-Meier method and compared by the log-rank test. Cardiac death was the only event considered in survival analysis. $P<0.05$ was considered significant.

Results
Of the 95 patients, 49 were randomized to training and 46 to nontraining. The baseline characteristics of the 2 groups are reported in the Table. There were no significant differences in age, site of MI, left ventricular ejection fraction, and extent of coronary artery disease. Likewise, there was no difference in exercise duration and peak heart rate. The mean value of BRS also did not differ at entry into the study between patients randomized to either group.

Both trained and nontrained groups increased their work capacity and peak oxygen consumption; however, these changes were greater in the trained group ($P<0.005$ and $P=0.02$ for work capacity, $P=0.002$ and $P=0.01$ for peak $\dot{V}O_2$). Also, peak heart rate at the same workload decreased, from 155±20 to 143±19 beats/min ($P<0.0001$) in the trained group and from 153±18 to 149±18 beats/min ($P=0.15$) in the nontrained group.

Changes in BRS after 1-month treatment are shown in Figure 1. Mean BRS increased significantly in the trained patients (by 26%, from 7.9±5.4 to 9.9±6.4 ms/mm Hg, $P=0.04$), whereas it did not change in the nontrained patients (-0.2%). Among trained patients, 16 of 49 (33%) increased BRS by ≥3 ms/mm Hg and thus represented the main focus of the analysis. Among nontrained patients, this occurred in 7 of 46 (15%). The data, split within the trained and nontrained groups, were also analyzed according to status of responders or nonresponders (BRS increase ≥3 ms/mm Hg or not). The parameters described in the Table were not different between the trained patients with a significant change in BRS (responders) and the group including the nontrained patients and those in whom physical training had no clear effect on BRS (nonresponders). Furthermore, the same parameters were not different within the trained and nontrained patients according to responder or nonresponder status.

Heart rate, recorded before exercise, decreased in both groups after the 1-month period, but the decrease tended to be

Baseline Clinical and Test Characteristics in the Two Groups

<table>
<thead>
<tr>
<th></th>
<th>Trained (n=49)</th>
<th>Nontrained (n=46)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>51±8</td>
<td>52±7</td>
<td>NS</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>51±13</td>
<td>51±14</td>
<td>NS</td>
</tr>
<tr>
<td>Anterior MI</td>
<td>20 (41)</td>
<td>20 (43)</td>
<td>NS</td>
</tr>
<tr>
<td>One-vessel CAD</td>
<td>16 (33)</td>
<td>16 (35)</td>
<td>NS</td>
</tr>
<tr>
<td>Multivessel CAD</td>
<td>5 (19)</td>
<td>5 (11)</td>
<td>NS</td>
</tr>
<tr>
<td>Exercise duration, min</td>
<td>12±3</td>
<td>13±4</td>
<td>NS</td>
</tr>
<tr>
<td>Peak heart rate, bpm</td>
<td>155±20</td>
<td>153±18</td>
<td>NS</td>
</tr>
<tr>
<td>BRS, ms/mm Hg</td>
<td>7.9±5.4</td>
<td>7.9±3.8</td>
<td>NS</td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrates</td>
<td>17 (35)</td>
<td>9 (20)</td>
<td>NS</td>
</tr>
<tr>
<td>$\beta$-Blockers</td>
<td>8 (16)</td>
<td>6 (13)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SD or n (%). CAD indicates coronary artery disease.
greater in the trained group (89.5±18.1 to 81.2±12.7, -8.3 beats/min, \(P=0.001\) versus 84.3±14.6 to 80.7±12.5, -3.6 beats/min, \(P=0.05\)), even though it reached the same level in both groups. Within the trained group, the decrease in heart rate was the same between responders and nonresponders (8.8 versus 7.2 beats/min), thus showing that it was related to exercise training. In contrast, in the nontrained group, only the 7 responders had an impressive reduction in heart rate compared with that of the 39 nonresponders (-12.0 versus -2.1 beats/min, \(P=0.048\)). This suggests that the recovery in vagal reflexes was associated with a spontaneous increase in tonic vagal activity, as grossly indicated by the resting heart rate. Blood pressure was similar between groups and subgroups at baseline and did not change after the 1 month of training or nontraining.

During the 10-year follow-up, cardiac death occurred in 6 of 49 trained patients (12%) and in 12 of 46 nontrained patients (26%) \((P=0.07)\). A nonfatal MI occurred in 2 patients in the nontrained group. Coronary artery bypass surgery was performed in 9 of 49 (18%) of trained and in 6 of 46 (13%) of nontrained patients.

When, by protocol, patients were grouped according to the occurrence of a significant training-induced increase in BRS, a striking difference in mortality was observed between the 2 groups, as shown in Figure 2. Although no patient died among the 16 in whom a significant improvement was observed in BRS, 18 (23%) patients died among the remaining 79 \((P=0.04)\). There was no difference in the incidence of revascularization procedures between the two groups (3 of 16, 19%, and 12 of 79, 15%, respectively).

To gather additional insight into the mechanisms involved, we looked for potential differences in survival associated with BRS increases among the nontrained patients and across groups. Within the nontrained group, there was 1 death among the 7 responders (14%) and 11 deaths among the 39 nonresponders (28%). When all responders and all nonresponders were grouped together independently of exposure to training, a significant difference emerged; namely, there was only 1 death among the 23 responders versus 17 deaths among the 72 nonresponders (4% versus 24%, \(P=0.04\)) (Figure 3). Of note, exercise capacity did not differ between these two groups; moreover, when changes in work capacity were examined among the patients who had not increased their BRS, it was observed that half of the deceased patients had at least a 50% increase in their work capacity.

**Discussion**

This prospective randomized study demonstrates that exercise training can significantly improve long-term prognosis among post-MI patients, provided that it shifts autonomic balance toward an increase of vagal activity in a quantitatively relevant manner.

The major implications of this finding are 2-fold. From the perspective of pathophysiology, it highlights the pivotal role of the autonomic nervous system in the improved survival associated with exercise training after a myocardial infarction and also shows that, for cardiac protection to ensue, this complex system has to be modulated effectively and in the right direction. From the clinical perspective, it provides a quantifiable physiological end point against which to titrate the exercise training program among post-MI patients, when the objective is the reduction of mortality and arrhythmic risk.

**Underlying Mechanisms**

Two main questions are elicited by the present results: how exercise-induced changes in BRS explain a mortality reduction and how they explain the persistence of the survival benefit during a 10-year follow-up. The first question can be thoroughly answered on the basis of our present understanding of the neural control of circulation, whereas for the second one, only speculations of varying probability can be offered.

An essential point for any analysis of these results is represented by the fact that, within this specific population, and possibly because of limited sample size, exercise training does not seem to be the only determinant of improved survival. Patients who increased or did not increase BRS by ≥3 ms/mm Hg did not differ when the traditional markers of adequate training were compared. It was the combination of exercise training and BRS increase that predicted increased survival. Still, it is worth noting that despite the relatively small population, exercise training resulted in a clear trend \((P=0.07)\) toward protection. This is in line with a recent report underscoring the relationship between exercise capaci-
ity and improved survival.\(^7\) However, an improvement in exercise capacity not paralleled by significant changes in BRS was often not accompanied by a better prognosis.

We also considered the possibility that an increase in BRS, even when occurring independently of training, might be associated with a reduced mortality risk. This analysis was prompted by an intriguing observation that we had previously made in post-MI dogs.\(^8\) Whereas dogs with depressed BRS at high risk for sudden cardiac death (so defined because of development of ventricular fibrillation during acute myocardial ischemia) had a BRS normalization after 4 weeks of exercise training and were protected from arrhythmias during a new ischemic episode, other high-risk dogs after 4 weeks of rest without training had no change in their depressed BRS and again developed ventricular fibrillation during a new ischemic episode. Within this latter group, however, there was one exception: one dog, for unknown reasons, had a complete BRS normalization and survived a new ischemic episode without arrhythmias. While being aware of its anecdotal value, we explored the possibility that something similar could happen in our patients. The results confirmed indeed that also among post-MI patients, whenever the autonomic status changes toward increased vagal activity, with or even without exercise training, cardiovascular mortality decreases. Not surprisingly, this autonomic shift is made more likely by exercise training.

Since our early observation that acute myocardial ischemia elicits an excitatory cardio-cardiac sympathetic reflex,\(^9\) which contributes to ischemic life-threatening arrhythmias,\(^10\) growing evidence has accumulated for the protective role against cardiac mortality offered clinically by both pharmacologic and surgical antiadrenergic interventions\(^11\) and experimentally also by interventions aimed at increasing vagal activity.\(^12\)–\(^14\) Exercise training was one of these interventions\(^15\) and is readily applicable to humans. The counterpart of the data on protection is offered by the multiple evidence that whenever patients with ischemic heart disease are found to have signs of impaired vagal activity by any of the many autonomic markers available (BRS, heart rate variability, postexercise heart rate recovery, and heart rate turbulence), they are also found to be at increased risk for cardiac mortality.\(^7\),\(^8\),\(^10\),\(^21\)–\(^24\)

Thus, the present evidence that exercise training is associated with increased survival only in conjunction with an adequate modulation of the autonomic balance toward increase in vagal activity, as revealed by the increase in BRS, is in line with our understanding of the relationship between the autonomic nervous system and cardiac function.\(^25\)

It is more difficult to explain the long-term protection afforded by the 1-month exercise training. In the absence of valid explanations, we can only offer 3 reasonable speculations that might serve as working hypotheses for future studies.

The first is that the initial randomization influenced subsequent behavior and that most patients randomized to training continued to exercise in the subsequent months and years whereas the other group did not. The second is that the rapid increase in vagal activity and decrease in sympathetic activity, indicated by the augmented BRS, may have altered the negative effects of ventricular remodeling in those patients who would have otherwise been destined to become at high risk. The third, and most intriguing, is that through the rapid increase in BRS, exercise training may have unmasked those patients who, before their MI, already had their autonomic balance tilted toward higher vagal and lower sympathetic activity and who for this very reason were already at lower risk for cardiac mortality after MI. This possibility, which supports the concept of at least a partial genetic control of autonomic responses,\(^26\) fits the experimental evidence that higher values of BRS before a myocardial infarction determined outcome during ischemic episodes after MI.

Previous Studies

Following our initial experimental evidence,\(^15\) several clinical investigations have observed increases in markers of vagal activity.\(^27\),\(^28\) One study,\(^29\) while reporting a BRS increase after exercise training, failed to demonstrate a difference with a control group; it was unfortunate that this control group had been assigned to a regimen of daily walking, thus voiding its value for comparison.

Despite several studies linking intense physical activity and lower rates of cardiac mortality both in primary and secondary prevention, the direct evidence of survival benefit with exercise training has been difficult to obtain. One such study showed that among 256 post-MI patients, a significant reduction in mortality during a 3-year follow-up period was observed in the subgroup with a LVEF <40%.\(^30\) Some of the reasons for this elusive relation were discussed by O’Connor et al\(^2\) and Cufrem et al.\(^3\) A confounding factor is that often changes in lifestyle are recommended to individuals entering a training program; to overcome this limitation, we provided both groups (trained and nontrained) with such recommendations, thus leaving exercise as the only randomized variable.

Clinical Implications

This study has direct clinical implications. By showing that, despite a favorable trend, exercise training per se is not sufficient for a statistically significant reduction in the risk for subsequent cardiac mortality but that it requires also the achievement of a shift in the autonomic balance, it provides a new therapeutic strategy. It thus provides a meaningful answer to the recommendation made in 1987 by the AHA Task Force on Sudden Cardiac Death—Nonpharmacologic Interventions.\(^1\) The availability of a quantifiable marker of autonomic balance to be modified by a certain amount and in a certain direction provides, in addition to exercise capacity,\(^17\) a target to guide the exercise training program in post-MI patients with the objective of reducing long-term cardiac mortality.

The uniqueness and main strength of the present study lie in having obtained the autonomic characterization of this patient population >15 years ago. Its main limitation is represented by the relatively small size of the group of patients randomized to exercise training and found to have also improved their BRS, on which rests the statistically significant evidence for long-term benefit. Nonetheless, the clinical relevance of the combination of the striking outcome...
with the feasibility of effectively reducing cardiac mortality by a low-cost nonpharmacologic means is too large to be overlooked.

References


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