Effects of a Residential Exercise Training on Baroreflex Sensitivity and Heart Rate Variability in Patients With Coronary Artery Disease
A Randomized, Controlled Study
Ferdinando Iellamo, MD; Jacopo M. Legramante, MD; Michele Massaro, MD; Gianfranco Raimondi, MD; Alberto Galante, MD

Background—Myocardial ischemia and infarction impair baroreflex sensitivity (BRS), which when depressed is predictive of future cardiac events after myocardial infarction (MI). The main objective of this study was to determine whether exercise training improves BRS in patients with coronary artery disease.

Methods and Results—Ninety-seven male patients with and without a previous MI were recruited after myocardial revascularization surgery and randomized into trained (TR) or untrained (UTR) groups. TR patients underwent a residential exercise program at 85% of maximum heart rate (HRmax) consisting of 2 daily sessions 6 times a week for 2 weeks. Eighty-six patients (45 TR and 41 UTR) completed the study. BRS was assessed at baseline and at the end of the protocol by the spontaneous baroreflex method. The standard deviation of mean R-R interval (RRSD) was also assessed as a measure of heart rate variability. At baseline, there were no significant differences between TR and UTR patients in any variable. In TR patients, BRS increased from $3.0 \pm 0.3$ to $5.3 \pm 0.7$ ms/mm Hg ($P<0.001$), RRSD from $18.7 \pm 1.4$ to $23.6 \pm 1.6$ ms ($P<0.01$), and R-R interval from $792.0 \pm 15.5$ to $851.3 \pm 20.5$ ms ($P<0.001$). No significant changes occurred in UTR patients. Increases in BRS and RRSD were significant in patients either with or without a previous MI.

Conclusions—Exercise training increases BRS and heart rate variability in patients with coronary artery disease. Improved cardiac autonomic function might add to the other benefits of exercise training in secondary prevention of ischemic heart disease. (Circulation. 2000;102:2588-2592.)

Key Words: reflex ■ heart rate ■ exercise ■ coronary disease

Patients with extensive coronary artery disease are at risk for life-threatening arrhythmias and sudden death. It is well recognized that alterations in the neural control of the heart characterized by decreased vagal activity and relative sympathetic predominance play a major role in the occurrence of arrhythmic events during myocardial ischemia or infarction. More specifically, several animal studies have indicated that a depressed baroreflex sensitivity (BRS), an index of the reflex vagal control of the sinoatrial node, and a reduced heart rate variability (HRV), considered as a measure of the tonic vagal control of the heart, are associated with a greater risk for ventricular fibrillation during transient ischemia after myocardial infarction (MI). The unfavorable effect of a depressed BRS on ventricular arrhythmias during myocardial ischemia also extends to animals without prior MI. Clinical studies have clearly demonstrated that both BRS and HRV are reduced after MI and that BRS is markedly depressed during spontaneous episodes of transient myocardial ischemia and in patients without an MI who experienced out-of-hospital ventricular fibrillation. Finally, a recent large prospective trial has definitively indicated that a reduced BRS has prognostic value for cardiac mortality and cardiac events after MI, independent of other risk factors (eg, low ejection fraction and serious arrhythmias). An emerging concept from the above studies is that strategies that increase these indirect markers of autonomic activity might be an important target for intervention in coronary artery disease.

Exercise training, as a part of a comprehensive rehabilitation program, has been shown to produce beneficial effects in many cardiovascular diseases and to improve prognosis after MI. In conscious dogs with or without a healed MI, exercise training was able to increase BRS and HRV, effects associated with a protective action against ventricular fibrillation during myocardial ischemia. Small clinical studies seem to confirm the effectiveness of exercise training in
improving some measures of HRV in post-MI patients.\textsuperscript{21–22} To date, there has been only 1 published study on the effect of exercise training on BRS in post-MI patients, and the results were not definitive.\textsuperscript{22} The effects of exercise training on cardiac autonomic function in coronary patients without previous MI have not been addressed.

The primary objective of the present study, therefore, was to determine whether a structured exercise training program improves BRS in coronary patients with or without a previous MI who had been referred to a formal rehabilitation program. The effect on HRV was also assessed.

### Methods

The study population consisted of patients with coronary artery disease referred after myocardial revascularization surgery to our cardiac rehabilitation center between January and December 1997. Patients had undergone CABG on the basis of symptomatic and/or abnormal findings on diagnostic procedures and arteriographically documented coronary artery disease. All patients came from the same cardiac surgery division, so that they had undergone the same surgical procedures and preoperative and postoperative clinical management.

Criteria for eligibility were male sex, in sinus rhythm, and with left ventricular ejection fraction \(\geq 50\%\), as determined by preoperative cardiac catheterization and by echocardiographic examination before hospital discharge and at the rehabilitation center. Exclusion criteria were age \(>70\) years, coexisting valvular and/or peripheral vascular diseases, concomitant endarterectomy, contraindications to exercise stress testing, frequent atrial or ventricular premature beats, conduction defects, insulin-dependent diabetes, arterial blood pressure \(>160/90\) mm Hg, pericarditis, peripheral neuropathy, orthopedic or neurological limitations, and perioperative MI or any serious postoperative complication.

The patients were admitted to the rehabilitation center during the first postoperative week, and after the initial screening, which included a 24-hour Holter recording, they were randomly assigned to a supervised, residential exercise training program (TR) or to an untrained group (UTR). Initially, 97 patients met the study criteria, but 7 dropped out from the study because of personal reasons (\(n = 5\)) or intercurrent illness (\(n = 2\)). Four patients were also excluded because of discomfort in breathing within the face mask that prevented measurements of gas exchange during the exercise stress test (\(n = 2\)) or for unexpected frequent premature beats at the time of recordings for autonomic evaluation (\(n = 2\)).

Eighty-six patients (45 TR and 41 UTR) completed the study. In post-MI patients, the time elapsed after MI ranged from 9 years to 2 months. However, in 66\% of patients, MI occurred in the last year before the study. Clinical characteristics of the patients are summarized in Table 1. Medications were not altered throughout the study. All patients gave written informed consent to participate in this study, which was approved by the Scientific and Ethical Committee of the rehabilitation center.

#### Protocol

Fourteen to 16 days after CABG, all patients underwent a functional (symptom-limited) incremental exercise test in the upright position on a bicycle ergometer (Corival 400, Lode) with monitoring of gas exchange (CPX). Exercise started with 1 minute of unloaded pedaling and increased by 20 W every 2 minutes. A 12-lead ECG and oxygen consumption (\(\text{Vmax} 29\) C, SensorMedics) were recorded continuously. At the end of the study, all patients repeated the symptom-limited exercise test.

#### BRS and HRV Assessment

BRS and HRV assessment was made the day before CPX and repeated after the training period. The patients were studied in the morning \(\geq 2\) hours after breakfast. Patients were studied at rest while supine in a quiet room at ambient temperature and were asked to relax and to avoid sleeping or talking. Recordings were begun after 10 to 15 minutes of acclimatization and were continued for 10 minutes. Patients were connected to an analogue multichannel signal conditioner and amplifier/filter (Marazza). The ECG signal was recorded from a precordial chest lead. Arterial blood pressure was continuously and noninvasively measured by Finapres (Finapres 2300, Ohmeda). This device provides accurate estimates of changes of intra-arterial pressure during laboratory tests, including the BRS testing used in the present investigation.\textsuperscript{23} The analogue signals were sampled at 300 Hz per channel and stored on hard disk for subsequent analyses.

BRS was dynamically assessed by the spontaneous baroreflex method.\textsuperscript{24} Details of this technique have been described previously.\textsuperscript{75–27} Briefly, beat-by-beat time series of systolic arterial pressure (SAP) and R-R interval are scanned by a computer to identify sequences of \(\geq 3\) consecutive beats in which SAP and R-R interval change in the same direction (either increasing or decreasing). A linear regression is applied to each individual sequence, similar to the technique that uses bolus injections of phenylephrine, and the mean slope of the SAP/R-R interval relationship, obtained by averaging all slopes computed within a given test period, is calculated and taken as a measure of spontaneous BRS for that period. This method allows a quantification of the BRS-cardiac reflex sensitivity at the current prevailing levels of arterial pressure and R-R interval and reflects vagally mediated baroreflex responses.\textsuperscript{24,28}

The time-domain measure of HRV considered in the present study was the standard deviation of mean R-R interval (RRSD).

#### Exercise Training Program

All patients resided at the rehabilitation center for a period of 3 weeks. Cardiac rehabilitation regimens lasting 2 to 4 weeks for patients in residential programs after a coronary event are standard in the Italian National Health Service. Before CPX, the program consisted of 2 daily sessions of calisthenics and walking. After CPX, the training program consisted of 2 daily sessions of 30 minutes of stationary cycling 6 times a week for 2 weeks (24 sessions overall) combined with calisthenics. Training intensity was graded according

### Table 1. Baseline Characteristics of Patients in the 2 Groups

<table>
<thead>
<tr>
<th></th>
<th>Trained (n=45)</th>
<th>Untrained (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean ± SD)</td>
<td>59.4 ± 7.8</td>
<td>58.5 ± 7.3</td>
</tr>
<tr>
<td>MI, n</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Time after MI, * mo</td>
<td>8.5 (4–31)</td>
<td>6.5 (3–24)</td>
</tr>
<tr>
<td>Site (anterior/inferior), n</td>
<td>13/9</td>
<td>15/7</td>
</tr>
<tr>
<td>Diseased vessels, n</td>
<td>2.6 ± 0.7</td>
<td>2.5 ± 0.6</td>
</tr>
<tr>
<td>(mean ± SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grafts, n</td>
<td>2.8 ± 0.9</td>
<td>3.0 ± 1.1</td>
</tr>
<tr>
<td>(mean ± SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>209.2 ± 33.5</td>
<td>205.4 ± 35.2</td>
</tr>
<tr>
<td>Smoking history, n</td>
<td>33</td>
<td>35</td>
</tr>
<tr>
<td>Medications, No. of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ca antagonists</td>
<td>25</td>
<td>21</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Vasodilators</td>
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<td>2</td>
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<tr>
<td>Amiodarone</td>
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<td>13</td>
</tr>
<tr>
<td>Diuretics</td>
<td>32</td>
<td>20</td>
</tr>
<tr>
<td>Antiplatelets</td>
<td>42</td>
<td>40</td>
</tr>
</tbody>
</table>
TABLE 2. Metabolic, Cardiovascular, and Autonomic Results at Baseline and After Training

<table>
<thead>
<tr>
<th></th>
<th>Trained</th>
<th>Untrained</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Peak oxygen uptake, mL</td>
<td>1287.3±38.5</td>
<td>1468.6±47.8†</td>
</tr>
<tr>
<td>Peak oxygen uptake, mL·kg⁻¹·min⁻¹</td>
<td>17.4±0.4</td>
<td>20.0±0.5†</td>
</tr>
<tr>
<td>SAP, mm Hg</td>
<td>119.2±2.1</td>
<td>124.6±2.7</td>
</tr>
<tr>
<td>DAP, mm Hg</td>
<td>62.8±1.6</td>
<td>64.5±1.6</td>
</tr>
<tr>
<td>R-R interval, ms</td>
<td>792.0±15.5</td>
<td>851.3±20.5†</td>
</tr>
<tr>
<td>BRS, ms/mm Hg</td>
<td>3.0±0.3</td>
<td>5.3±0.7†</td>
</tr>
<tr>
<td>RRSD, ms</td>
<td>18.7±1.4</td>
<td>23.6±1.6*</td>
</tr>
</tbody>
</table>

Values are mean±SE. DAP indicates diastolic arterial pressure. *P<0.01; †P<0.001 vs baseline.

to 85% of the maximum heart rate (HRmax) attained in the initial CPX (or to 75% of HRmax in patients older than 65 years). Heart rate (HR) was tracked by a Polar chest-belt HR monitor (Polar Electro Oy) that simultaneously controlled the computer-driven workload of the bicycle ergometer (Bikerace, Technogym) to maintain the target HR.

Subjects in the control group continued to perform walking and calisthenics with the same daily schedule as the TR group for 2 weeks as inpatients. The activity for the control group was not designed to improve cardiovascular performance. All sessions were held under the supervision of a cardiologist.

Statistical Analysis

Differences in baseline characteristics between TR and UTR groups were evaluated by χ² and unpaired t tests. Within-group changes in the reported variables were evaluated by paired t test or Wilcoxon signed rank test for nonnormally distributed variables. Between-group comparisons were performed by unpaired t tests and Mann-Whitney rank sum test. Relations between variables were assessed by Pearson product-moment correlation. Data were expressed as mean±SE unless otherwise specified. Statistical significance was assumed at P<0.05.

Results

There were no significant differences in baseline characteristics between TR and UTR patients with respect to all variables, including peak Vo₂, arterial pressure, R-R interval, RRSD, and BRS (Tables 1 and 2).

Exercise training resulted in a significant increase in peak Vo₂ (Table 2). A small increase in peak Vo₂ was also observed in the UTR group and can be explained in part by normal recovery from surgery and by the fact that our controls performed some amount of daily physical activity. However, the magnitude of Vo₂ increase was significantly and markedly greater in the TR group (181.3±27.2 versus 73.9±18.0 mL/min, P=0.001). In TR patients, resting R-R interval was significantly increased by 7%, BRS by 73%, and RRSD by 26%. No significant changes in these variables were observed in UTR patients (Table 2).

No correlations were found between peak Vo₂ and BRS either at baseline for the study population as a whole (r=0.18, P=0.10) or after training in the TR group (r=0.09, P=0.55). Similarly, no relationships were found between peak Vo₂ and RRSD at baseline in the whole population or after training in the TR group (r=0.15, P=0.16 and r=0.11, P=0.49, respectively).

No significant differences were observed in baseline BRS and RRSD between MI and non-MI patients in the overall population. BRS was 3.4±0.4 versus 3.0±0.3 ms/mm Hg and RRSD was 18.0±1.3 versus 17.9±1.3 ms in MI and non-MI patients, respectively. Mean age did not differ significantly between MI and non-MI patients (59.0±6.6 versus 58.9±8.5 years), nor did the number of coronary vessels with a critical stenosis (2.4±0.7 versus 2.6±0.6). BRS increased significantly in both MI and non-MI trained patients, as did RRSD (Figure), and the magnitude of the increase in both variables did not differ significantly between the 2 groups (2.8±1.0 versus 1.7±0.5 ms/mm Hg, P=0.53 and 5.4±2.3 versus 4.3±1.8 ms, P=0.72, for BRS and RRSD, respectively).

No significant cardiovascular events occurred during the training sessions.

Discussion

The present study indicates that a structured exercise training program is able to enhance BRS and increase HRV in patients...
with coronary artery disease. The relevance of this finding should be placed in the context of the growing evidence indicating the adverse effect of a depressed vagal cardiac modulation and the protective role exerted by high vagal activity in the setting of ischemic heart disease.

Animal studies have clearly indicated that the presence of depressed vagal reflexes and enhanced sympathetic activation is associated with a greater risk for life-threatening arrhythmias during myocardial ischemia. Clinical studies confirmed the adverse effect of impaired vagal modulation by showing that both BRS and HRV are reduced early after MI and that this has an independent prognostic value. Moreover, a depressed BRS may play a role in the occurrence of malignant arrhythmias, even long after MI.

Conversely, interventions capable of increasing vagal activity exert a protective effect against ischemia-related arrhythmias. Among these interventions, exercise training has been shown to increase both BRS and HRV and to prevent ventricular fibrillation, concomitantly improving cardiac electrical stability, in conscious dogs with and without healed MI. Thus, exercise training might be an effective nonpharmacological tool to increase the vagal contribution to autonomic control of the heart in patients with coronary artery disease, as has been observed in other pathological states. Indeed, recent studies have suggested the effectiveness of exercise training in improving HRV in post-MI patients, and this was confirmed by the present investigation. However, the potential for exercise training to improve BRS in patients with coronary artery disease had not been clearly established. One small study reported an improvement in BRS after exercise training in post-MI patients, but the lack of an untrained control group prevented a definitive conclusion from being reached. Thus, this is the first randomized, controlled study obtained in a relatively large population showing that exercise training results in marked enhancement of both BRS and HRV in patients with coronary artery disease. This is important information, because BRS and HRV reflect different, although possibly related, aspects of autonomic control of the heart in patients with coronary artery disease. The relevance of this finding should also be considered.

The results of the present study also indicate that the improvement of BRS associated with exercise training is not limited to patients with prior MI but extends to coronary patients without MI, in whom measures that could reduce the risk of subsequent lethal events might be of paramount importance. The potential clinical relevance of increasing BRS in coronary patients without MI is also outlined by the observation that a depressed BRS present before MI affected the susceptibility to ventricular fibrillation during myocardial ischemia that occurred after MI in an animal model of sudden death.

No significant differences were observed in baseline BRS between patients with and without a previous MI. This finding could be explained by the severity of coronary artery disease, which was similar in MI and non-MI patients, as evaluated by the number of vessels with critical stenosis, the extent of coronary narrowing negatively affects BRS.

Our study confirms the improvement in cardiovascular performance induced by exercise, and the 14% increase in peak $\dot{V}O_2$ obtained after this short-term yet intensive, concentrated endurance exercise training is in line with expectations. However, no relationship was observed between changes in functional capacity and indexes of autonomic function after training, a finding that is in line with the hypothesis that the mechanisms responsible for the improvements may differ for each variable. The mechanisms through which exercise training affects these markers of cardiac vagal modulation are still unclear and cannot be defined by the present investigation. They may involve adaptations in peripheral and central neural pathways, although modifications in the responsiveness of the heart might also contribute.

Some possible limitations of the present investigation deserve comment. The first is the generalization of the reported effects to other coronary patient populations, namely, those who have not undergone CABG. However, it is reasonable to speculate that the benefits of exercise training should also extend to patients who have not undergone CABG but are eligible for a formal exercise training program. Moreover, there are no data indicative that CABG per se positively affects BRS and HRV in patients without MI or in the recovery phase after MI. Consistent with this assumption is the lack of spontaneous increase in BRS and HRV in the control group. In any case, the patients of the present study are representative of a large population of ischemic patients for whom cardiac rehabilitation is highly recommended and who could benefit from improved cardiac autonomic function.

Second, we do not know whether improving markers of autonomic activity by exercise actually affects the outcome of patients with coronary artery disease. The present study was not designed for this purpose. Instead, it was aimed at addressing the question of whether exercise training improves autonomic markers that have been shown to carry adverse effects and negative prognosis in ischemic heart disease. The answer to this question is affirmative. In fact, the increase in BRS is in a direction that has been associated with a better outcome in coronary patients. However, the potential for exercise-induced enhancement of BRS and HRV to improve the risk profile in coronary artery patients remains to be demonstrated. This would require a large, multicenter trial. Nevertheless, among the many beneficial effects of exercise training in secondary prevention of ischemic heart disease, improvement in markers of cardiac autonomic function should also be considered.
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