Effects of cardiac rehabilitation and exercise training on autonomic regulation in patients with coronary artery disease

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Background Although cardiovascular rehabilitation and exercise training have substantial benefits in various ischemic heart disease (IHD) risk factors and subsequent prognosis after major IHD events, there is a paucity of information about its effects on autonomic regulation (such as heart rate variability [HRV] and baroreflex gain), particularly considering its arterial and cardiopulmonary components.

Methods We studied 40 patients (aged 60 ± 6 y) after major IHD events, including 29 who underwent a comprehensive phase II cardiac rehabilitation and exercise training program and 11 controls who did not attend cardiac rehabilitation. Specifically, we determined whether active training improves prognostic indices of autonomic regulation of the SA node and whether changes in baroreflex gain could be ascribed to the arterial or to the cardiopulmonary component of the overall arterial pressure/heart period baroreflex.

Results Only patients with IHD undergoing active rehabilitation demonstrated a significant increase in R-R interval, in its variance, in overall gain of arterial pressure/heart period baroreflex (7.44 ± 1.20 ms/mm Hg to 12.12 ± 1.48 ms/mm Hg, P < .001) and in peak oxygen consumption (Δ = 2.45 mL/kg/min, P < .001). Separate examination of the selective arterial and cardiopulmonary components showed that only the latter increased significantly (6.17 ± 1.09 ms/mm Hg to 10.62 ± 1.56 ms/mm Hg; P < .01).

Conclusions Cardiac rehabilitation is associated with significant improvements in autonomic markers of neural regulation of the SA node, such as increases in R-R variance and the gain of the overall spontaneous baroreflex, with specific improvements in the cardiopulmonary component as opposed to the arterial baroreflex component of this system. These improvements may further explain the reduction in morbidity and mortality noted after formal cardiac rehabilitation and exercise training programs. (Am Heart J 2002;143:977-83.)

Autonomic dysfunction, as evidenced by reduced heart rate variability and baroreflex gain, has strong adverse effects on subsequent clinical outcome in patients with ischemic artery disease (IHD), offering a potential functional rationale to the beneficial effects of therapeutic modalities such as β-adrenergic receptor blockade, which may be capable of ameliorating attending autonomic alterations.

We and others have described the numerous benefits of cardiac rehabilitation and exercise training programs in patients with IHD and congestive heart failure (CHF), including improvements in exercise capacity, clinical and psychological factors, and marked reduction in subsequent major cardiac morbidity and mortality, including total mortality. However, there is a paucity of information regarding the effects on autonomic regulation, and notably on baroreflex mechanisms, which have been reported to be either improved, unaffected, or depressed by cardiac rehabilitation and exercise training. On the contrary, in other cardiovascular conditions, such as in hypertension, consistent data suggest that exercise training improves baroreflex gain. These contradicting results might well depend on technical aspects such as the intensity and type of exercise training routines.
used or on the methods used to assess baroreflex gain.20

A simplified open-loop linear model21 is commonly used to approximate the arterial pressure/heart period relationship, in spite of the well-recognized closed-loop properties of the intact circulation. The presence of several interacting influences, such as respiration and sympathetic activity,22 may be particularly important in various disease conditions including IHD1 and CHF,23 reducing the accuracy of a simple linear open-loop model in assessing the arterial pressure/heart period relationship. The application of a trivariate model21 that uses the components of spontaneous beat-by-beat variability of the R-R interval, systolic arterial pressure, and respiration, provided a unitary view20 of the arterial pressure/heart period relationship explicitly addressing respiratory influences. The advantage of this trivariate system is its ability to separate the indices of arterial and cardiopulmonary baroreflex gain,25 as well as the factors influencing feed forward pathways.26

In this study of vigorously treated stable patients with IHD, we assessed the effects of formal outpatient phase II cardiac rehabilitation and exercise training programs on parameters of autonomic function. Specifically, we determined whether active training improves prognostic indices of autonomic regulation of the SA node (heart rate variability [HRV] and spontaneous baroreflex gain) and whether changes in baroreflex gain could be ascribed to the arterial or to the cardiopulmonary component of the overall arterial pressure/heart period baroreflex.

Methods
Study population
This study involved 40 consecutive patients from Ochsner Medical Institutions, referred to the Cardiovascular Health Center for comprehensive phase II cardiac rehabilitation and exercise training after a major cardiac event, including myocardial infarction (MI), coronary artery bypass grafting (CABG), or percutaneous balloon angioplasty (PTCA).

Patients were subdivided into 2 groups: 29 patients (15 CABG, 9 MI, 5 PTCA) attended and completed the 12-week outpatient phase II cardiac rehabilitation and exercise training programs (Cardiac Rehab group), and 11 patients (3 CABG, 4 MI, 4 PTCA) declined to participate in the program but agreed to participate as controls (Control group). All patients received statistically similar medical therapy including β-adrenergic blocking agents, angiotensin-converting enzyme inhibitors, calcium-channel blockers, diuretics, lipid medications and aspirin, which were given for ≥4 weeks before study entry and were maintained throughout the study program (Table I).

<table>
<thead>
<tr>
<th>Study population</th>
<th>Cardiac rehab</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>29</td>
<td>11</td>
</tr>
<tr>
<td>Age (y)</td>
<td>63 ± 1.97</td>
<td>53 ± 2.38*</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>24/5</td>
<td>8/3</td>
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<tr>
<td>Weight (kg)</td>
<td>75.2 ± 2.01</td>
<td>90.6 ± 5.88*</td>
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<tr>
<td>Height (cm)</td>
<td>173 ± 3</td>
<td>175 ± 3</td>
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<tr>
<td>Percent body fat</td>
<td>22.6 ± 0.9</td>
<td>29.7 ± 4.1</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>192 ± 9</td>
<td>210 ± 12*</td>
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<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>35.0 ± 1.9</td>
<td>42.9 ± 3.6*</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>116 ± 6</td>
<td>135 ± 11*</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>170 ± 15</td>
<td>162 ± 20</td>
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<tr>
<td>Exercise capacity, estimated METs</td>
<td>7.3 ± 2.1</td>
<td>4.95 ± 0.3</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>112 ± 10.4</td>
<td>105 ± 11</td>
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<tr>
<td>VO2 (mL/kg/min)</td>
<td>18.1 ± 0.9</td>
<td>18.0 ± 1.0</td>
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<tr>
<td>LV end diastolic diameter (cm)</td>
<td>4.9 ± 0.3</td>
<td>4.5 ± 0.3</td>
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<tr>
<td>Ejection fraction (%)</td>
<td>50 ± 3</td>
<td>51 ± 4</td>
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<tr>
<td>β-Blockers (%)</td>
<td>18 (62)</td>
<td>6 (55)</td>
</tr>
<tr>
<td>ACE inhibitors (%)</td>
<td>6 (21)</td>
<td>3 (27)</td>
</tr>
<tr>
<td>Calcium antagonist (%)</td>
<td>9 (31)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>ASA (%)</td>
<td>16 (55)</td>
<td>8 (73)</td>
</tr>
<tr>
<td>Diuretics (%)</td>
<td>4 (14)</td>
<td>2 (17)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SE  
*P < .05 cardiac rehabilitation group versus control group.

Protocol
Protocol, data collection, and statistical analysis were performed as previously described.5,6 Patients were referred to and participated in outpatient phase II cardiac rehabilitation lasting 12 weeks and consisting of 36 educational and exercise sessions. Each session consisted of approximately 10 minutes of warm-up exercises, including stretching and calisthenics, followed by 30 to 40 minutes of continuous upright aerobic and dynamic exercise (various combinations of walking, bicycling, jogging, rowing, etc), light isometric exercise (ie, hand weights), and approximately 10 minutes of cool-down stretching and calisthenics. Exercise intensity was prescribed individually so that the patient’s heart rate was approximately 70% to 85% of the maximum heart rate and targeted below anaerobic threshold, which was determined on the entry cardiopulmonary stress test, or 10 to 15 beats per minute below the level of any exercise-induced symptomatic or silent myocardial ischemia. In addition to the supervised exercise sessions, all patients were encouraged to exercise approximately 1 to 3 times per week outside of the formal program. Each patient’s exercise prescription was periodically adjusted to encourage a gradual increase in overall exercise performance.

At baseline, patients were instructed to comply with the Phase I diet of the American Heart Association. Patients were frequently reinforced by physicians, dietitians, nurses, and exercise physiologists to comply with both the exercise and dietary portions of the program throughout its duration. Group sessions were held on educational aspects of IHD and psychological adaptation to this disease. Anthropometric and metabolic data, peak oxygen consumption (VO2), and autonomic function were assessed at baseline (approximately 36 weeks after the cardiac event; average 4 weeks) and again one week after completing the cardiac rehabilitation and exercise training program. Ejection fraction was assessed by
echocardiography in each patient only at baseline because left ventricular performance appears largely unaffected by exercise training in IHD. 27

Control group

After completing the initial data collection, the control group subjects maintained their normal levels of daily physical activity. They received informational material and suggestions on how to improve their lifestyle, and no active intervention was performed. At the time of the second recording, verification of lack of significant exercise was obtained from patients through self report.

Study of the autonomic control of the circulation

On the day of the study, subjects were instructed to avoid alcohol and caffeinated beverages for the 12 preceding hours, to avoid heavy physical activity the day before, and to come to the laboratory between 7:00 AM and 12:30 PM, after a light breakfast. All subjects were carefully instructed about the study procedure and all gave informed consent to a protocol approved by the Ochsner Medical Institutions institutional review board. Patients were studied in resting conditions (lying down with 15 degree back support); after a 10-minute period to allow for stabilization, 10 minutes of data were obtained.

Recorded variables

By use of standard Ag-AgCl electrodes and a piezoelectric respiratory belt (PVT2, 3M, Austin, Tex), both the electrocardiogram (CM5) and the respiratory signal were monitored with a 2-way radiotelemetry system (Marazza, Monza-Milano, Italy). The arterial pressure waveform was continuously estimated noninvasively with a plethysmographic device (Finapres, Ohmeda, Englewood, Colo). Data were acquired on the hard disk of a personal computer equipped with an analogue-to-digital board (Data Translation, Marlboro, New Hampshire) with an acquisition rate of 300 samples/channel/second.

Data analysis

The principles and software for data analysis have already been described in detail. 28–29 Briefly, from an electrocardiogram derived tachogram, an optimized autoregressive approach furnished the power and center frequency of low frequency (LF) and high frequency (HF) spectral components, in both absolute (ms²) and normalized (nu) units. With this approach, the LF component of R-R interval variability, in nu, provides a quantitative index of sympathetic excitatory modulation of the SA node, and the HF component is a marker of vagal modulation. 28–29 The LF/HF is a convenient marker of sympathovagal interaction. The LF component of sympathetic arterial pressure variability provides a marker of sympathetic vasomotor modulation. 28–29 Spectral analysis was also performed on the respiratory signals to assess the main respiratory frequency. From the simultaneous analysis of arterial pressure and R-R interval variabilities, a frequency domain index (αlumped) can be derived (a measure of the overall gain of the arterial pressure/heart period relationship that provides results similar to those obtained with the phenylephrine slope approach). 19 A trivariate model originally proposed by Baselli et al 24 was used to selectively evaluate the gain of the arterial baroreflex loop (αart). This model describes the closed loop relationship between R-R interval, systolic arterial pressure variability and respiration by use of a generalized least square approach. 30 After identification, the transfer function describing the causal influences of systolic arterial pressure on R-R interval provides an estimate of the arterial baroreflex gain αart. On the basis of recent studies indicating that a simple additive model applies to the relationship between arterial and cardiopulmonary components of baroreflex regulation of the SA node, 31 the difference between αlumped and αart was taken as an approximate indicator of the reflex influence of cardiopulmonary baroreceptor loops on beat-by-beat control of heart-period (αcpr). 20–25

Statistical analysis

Data are presented as mean ± SEM. Significance of differences in data were assessed with 2-factor (group and time) analysis of variance for repeated measures, according to either the t test or Coch, by use of the Geisser-Greenhouse correction as appropriate. A P value < .05 was considered significant.

Results

Study population

At baseline (Table I), statistically significant differences were noted between cardiac rehabilitation and control patients regarding age, obesity indices, and plasma lipids. However, both groups were statistically similar in regards to sex, blood glucose, LV end-diastolic volume, ejection fraction, exercise capacity as assessed by peak VO₂, and pharmacologic treatments. After cardiac rehabilitation and exercise training, patients had statistically significant improvements in triglycerides (Δ = −26.1 ± 11.0 mg/dL, P < .02), and peak VO₂, which increased significantly (Δ = 2.45 ± 0.5 mL/kg/min). Changes in VO₂ were significantly correlated with increases in R-R variance (P < .05), but not with indices of baroreflex gain. Improvements in other parameters, however, were not statistically significant. There were no statistically significant changes noted over time in the control patients.

Hemodynamics

At baseline, R-R interval and systolic arterial pressure (SAP) values were similar in the 2 patient groups. After formal cardiac rehabilitation and exercise training, a significant increase in R-R interval was noted, whereas no significant changes were observed in SAP values. There were no changes in either R-R intervals or SAP values in control patients (Table II).

Autonomic control of the circulation

Spectral analysis. At baseline, there were no significant differences in spectral parameters between groups, with the exception of R-R interval variance,
which was greater in the younger control patients. After cardiac rehabilitation and exercise training, significant increases were noted in the R-R interval variance, reaching values slightly greater than those observed in the control group (Table II).

**Baroreflex gain.** At baseline, a significant difference between groups was noted in $\alpha_{\text{lumped}}$, which was greater in the younger control patients. After cardiac rehabilitation and exercise training programs, significant increases were noted in $\alpha_{\text{lumped}}$ from 7.44 ± 1.29 ms/mm Hg to 12.12 ± 1.48 ms/mm Hg ($P < .001$). On the other hand, this index diminished slightly in the control group.

The index $\alpha_{\text{ort}}$, a marker of the arterial baroreflex gain, was unchanged in both active and control patients. Conversely, $\alpha_{\text{cp}}$, a marker of cardiopulmonary baroreflex gain, increased significantly, from 6.17 ± 1.09 ms/mm Hg to 10.62 ± 1.56 ms/mm Hg ($P < .01$), in the cardiac rehabilitation group and decreased slightly in the control group (Table III and Figure 1).

**Respiration.** Respiratory rate and pattern, assessed with spectral analysis of respiratory movements, were not significantly different in the 2 groups considered at baseline, and were not modified by either cardiac or sham rehabilitation (Table II).

**Discussion**

This study shows significant improvements in parameters of autonomic function after formal phase II outpatient cardiac rehabilitation and exercise training programs, as indicated by significant increases in R-R, R-R variance, and in the gain of the arterial pressure/heart period relationship. This latter increase appears ascribable to a selective improvement of the cardiopulmonary component of the baroreflex while the arterial component remains unaffected. Because autonomic dysfunction is known to adversely affect clinical outcome in patients with cardiovascular diseases,$^{1,2}$ these improvements in autonomic regulation after cardiac rehabilitation may add to the other proven benefits of cardiac rehabilitation and exercise training in improving subsequent prognosis of these patients with IHD.

It should be noted that the usual methods$^{21}$ used to assess baroreflex gain in a clinical setting are based on a simplified linear open loop model that only considers arterial reflexogenic areas as a sensory input. However, it is well recognized that the relationship between ar-
terial pressure and heart period is complex and derives from the interplay of several neural and non-neural mechanisms acting in a closed loop. For instance, sympathetic and cardiopulmonary afferents might play an important modulating role in baroreflex gain, whereas respiration may add an important bias because of its direct effects on cardiac vagal motoneurons, as indicated in the early description of the Oxford method.

On the basis of prior data from human investigations showing that an additive model (considering changes in carotid, aortic and cardiopulmonary pressures) accounts for the major fraction of R-R variability, we have recently described a method to disentangle arterial from nonarterial (ie, mostly cardiopulmonary) components of the overall baroreflex gain. This approach led to the observation, obtained in this investigation, of a selective improvement of the cardiopulmonary baroreflex gain after training in patients with IHD. The observed changes are unlikely to depend on changes in left ventricular performance, which appear to be largely unaffected by exercise training in patients with IHD. Incidentally, left ventricular function, as assessed by ejection fraction, was similar at entry in our 2 patient groups. Extrapolating from data obtained in athletes, an improved cardiopulmonary baroreflex could be the result of an augmented inhibitory influence of cardiopulmonary receptors possibly linked to the improved respiratory performance. Likewise, training induced an improved cardiac neuronal function, in the absence of changes in left ventricular performance, in patients with CHF. A likely role of more powerful vagal mechanisms after exercise training is further suggested by the increase in R-R interval and R-R variance observed in this study in the cardiac rehabilitation group. Notably, in this study, only insignificant changes were observed in the spectral profile of HRV, possibly reflecting the influence of maintained medical treatment as well as the fact that the exercise training routine was of only moderate intensity. More intense training or more severe cardiac functional impairments at baseline might instead lead to a more apparent variation in spectral profile. For instance, Coats et al showed a reduction in LF from elevated baseline values in patients with CHF who were subjected to a period of physical training. Opposite changes were observed for HF. In line with data from patients with CHF, we also observed, in this investigation, that the improved exercise performance (assessed by increased peak VO2) correlated with increases in R-R variance. However, the lack of correlation with other autonomic markers (such as baroreflex gain) and the nonsignificant variations in spectral profile induced by active training point to either an inhomogeneous influence of cardiac rehabilita-

tion, or to the importance of baseline alterations in neurovegetative regulation mediated by heart failure.

Although the exercise training component is often emphasized in discussions regarding cardiac rehabilitation, it should be recalled that the phase II outpatient cardiac rehabilitation program is a multifunctional risk factor prevention program that includes dietary and educational interventions, with emphasis on various psychological factors and stress management. Although the role of these various components of the cardiac rehabilitation program were not addressed separately in this study, because mental stress can reduce baroreflex gain, it is quite possible that the stress management component may have contributed to the favorable results that we have described. Cardiac rehabilitation and exercise training programs provide benefits, in addition, on various psychological functions, especially depression, hostility, and overall psychological distress that might further improve prognosis.

Several study limitations need to be emphasized. First, all patients were not randomized, but referred to the cardiac rehabilitation program, which in itself raises the possibility of selection bias, although, for patients who have a cardiac event, there is an almost 100% referral rate to the cardiac rehabilitation pro-
grams at our institution. The control group represented patients who chose not to attend the program. Moreover all patients received standard medical therapy including β-adrenergic blocking agents, angiotensin-converting enzyme inhibitors and calcium-channel blockers that could affect autonomic markers.14 However, this is an unlikely major bias because treatment distribution was similar in the 2 groups and all patients maintained the same treatment throughout the study program. Finally, the control patients were younger, heavier, and had higher levels of total low-density lipoprotein and high-density lipoprotein cholesterol. However, most autonomic variables at baseline were similar in both groups, although the younger control patients had greater R-R interval variance and αdamped compared with the treatment group. Nevertheless, the treatment group demonstrated marked improvements in many variables after the cardiac rehabilitation and exercise training program, whereas no significant changes were noted in the control group.

Accordingly, we believe that our data suggest that in medically treated IHD patients, a standardized outpatient phase II cardiac rehabilitation and exercise training program produces beneficial effects not only on exercise capacity and plasma lipids, but also improvements in autonomic markers of neural regulation of the SA node, such as increase of R-R variance and of θ component25 of the arterial pressure and heart period relationship, whereas the arterial baroreflex component seems unaffected. These improvements in autonomic function after outpatient cardiac rehabilitation and exercise training may help to further explain the effects of this therapy to reduce subsequent clinical events and mortality,9 which seem out of proportion to the rather modest improvements generally noted in the overall IHD risk profile.

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References


