Autonomic Nervous System Adaptations to Short-term Exercise Training*

Maria Teresa La Rovere, M.D.; Andrea Mortara, M.D.; Giulia Sandrone, M.D.; and Federico Lombardi, M.D.

Signs of sympathetic hyperactivity and low parasympathetic activity have been found during the acute and recovery phases of myocardial infarction and have been associated with an increased risk of cardiac mortality. Beneficial effects of physical training have been recently reported in post-myocardial infarction patients. We tested the hypothesis that physical training would be effective in improving the autonomic balance by studying 22 patients with a first and recent myocardial infarction who were randomly assigned to enter or not enter a 4-week in-hospital physical training program. Spectral indices of heart rate variability were analyzed at rest and during 70° head-up tilt before and after the index training, not training period. As expected, physical training induced a significant increase in exercise duration (13.7 ± 0.9 vs 17.1 ± 0.1 min, p<0.001) and in the anaerobic threshold (9.5 ± 0.7 vs 12.0 ± 1.0 min, p<0.02) in trained patients, while no changes were observed in the untrained group. At entry, in both groups, spectral profile of heart rate variability was characterized by a predominant LF component and a smaller HF component with no further modification after head-up tilt. After 4 weeks, in resting conditions, no significant changes in spectral components were observed in both trained and untrained patients. After physical training, head-up tilt produced significant modifications in spectral profile with an increase in the LF component (84±3 vs 69±5 nu, p<0.01) and a decrease in the HF component (7±1 vs 19±4 nu, p<0.05) in trained patients, while no changes were observed in the untrained patients. Our data suggest that in postmyocardial infarction patients, 4 weeks of physical training may induce an improvement in the autonomic balance with a restoration toward normal in the reflex activity of the system.

It is well-established that myocardial infarction (MI) can affect the autonomic balance to the heart1 and changes in sympathovagal balance and impaired baroreceptor function can be detected early in the course of infarction.4-7 Enhanced sympathetic activity and reduced parasympathetic cardiac outflow have been associated with the emergence of ventricular arrhythmias in the presence of ischemia8-10 and a prognostic relevance of disordered autonomic function has been addressed both at experimental and clinical level11-15 in the postinfarction period by several methods.

Regularly performed exercise is generally thought to improve cardiovascular performance and the beneficial effects of physical training in reducing mortality after myocardial infarction have been recently documented from meta-analysis studies.16,17 The mechanisms of the training-induced regulatory changes have not been completely delineated. Adaptations in the autonomic nervous system have been considered to be responsible for the resting and submaximal exercise bradycardia found after physical training, but data are still conflicting on the relative role of sympathetic and parasympathetic influences.

The primary goal of our study was to determine whether physical training would evoke changes in the autonomic tone in subjects surviving a recent myocardial infarction.

METHODS

Patients

The study population consisted of 22 male patients suffering from a first and recent myocardial infarction who were randomly assigned to enter or not enter a supervised physical training program.

Patients were excluded from randomization if they were older than 70 years, had arterial blood pressure of more than 160/90 mm Hg, had insulin-dependent diabetes, had atrial fibrillation or abnormal sinus node function, or had exercise-induced myocardial ischemia. All patients were in NYHA class.

The trained (T) and untrained (UT) patients did not differ in mean age (47±6 years vs 54±10 years) and site of myocardial infarction (5 anterior myocardial infarctions vs 5 anterior myocardial infarctions).

A maximal symptom-limited exercise stress testing and 24-h ECG recording were performed at 4 and 8 weeks after the acute myocardial infarction, in pharmacologic wash-out. All subjects gave informed consent to the study.

Exercise Protocol

Maximal symptom-limited exercise tests were performed in upright position on bicycle ergometer with an initial work load of 25 W, with subsequent increments of 25 W every 3 min. Exercise was terminated whenever angina, dyspnea, exertional hypotension, ventricular tachycardia, exhaustion, ST segment elevation or depression equal to or more than 2 mm occurred. Oxygen consumption and carbon dioxide production were measured with an oxygen and carbon dioxide analyzer (Oxycon IV, Mijnhardt) after each minute of exercise.

The exercise test variables analyzed included duration of exercise (min), heart rate at rest and at the same work load, double product at same work load, anaerobic threshold in minutes, defined according to non invasive gas exchange criteria.9

24-h ECG Recording

The patients were connected to a 2-channel ECG recorder (Avionics 465), and 2 modified CM1 and CM5 leads were recorded for 15 min in resting condition and for 15 min with the subjects tilted at 70°. The ECG recording was continued during the following 24 h in hospitalized but unrestricted condition.
Table 1 — Ergometric Data at 4 and 8 Weeks in Untrained (UT) and Trained (T) Patients

<table>
<thead>
<tr>
<th></th>
<th>ED, min</th>
<th>HR Rest, Beats min⁻¹</th>
<th>HR SWL, Beats min⁻¹</th>
<th>DF SWL, mm Hg beats min⁻¹</th>
<th>AT, min</th>
</tr>
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<tbody>
<tr>
<td>UT</td>
<td></td>
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<tr>
<td>4 Weeks</td>
<td>14.6 ± 0.6</td>
<td>75 ± 4.2</td>
<td>155 ± 6.3</td>
<td>28,520 ± 1,534</td>
<td>11.4 ± 0.5</td>
</tr>
<tr>
<td>8 Weeks</td>
<td>14.7 ± 0.7</td>
<td>74 ± 3.3</td>
<td>148 ± 5.4</td>
<td>27,800 ± 1,412</td>
<td>11.3 ± 0.6</td>
</tr>
<tr>
<td>T</td>
<td></td>
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<tr>
<td>4 Weeks</td>
<td>13.7 ± 0.8</td>
<td>83 ± 4.2</td>
<td>165 ± 2.7</td>
<td>29,909 ± 1,379</td>
<td>9.5 ± 0.7</td>
</tr>
<tr>
<td>8 Weeks</td>
<td>17.0 ± 1.0</td>
<td>80 ± 3.6</td>
<td>152 ± 3.1</td>
<td>27,120 ± 1,330</td>
<td>12.0 ± 1.0</td>
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</table>

*ED = exercise duration; HR at rest = heart rate at rest; HR at SWL = heart rate at same work load; DP at SWL = double product at same work load; AT = anaerobic threshold.

tp<0.001.

$p<0.02.$

$p<0.05.$

Data were analyzed by a minicomputer (PDP 11/24). Twenty-four-hour ECG recordings were played back at 60 times real time, and the analog to digital conversion was performed at 18,000 samples/s to achieve a real time AD conversion of 300 samples/s. The principles of the software for data acquisition and spectral analysis have already been described.1,2 From the surface ECG, the computer program calculates a series of 512 consecutive intervals as a function of beat numbers, thus obtaining the tachogram. From each series, simple statistics (mean and variance) and the autoregressive coefficients necessary to define the best estimate of the power spectral density are calculated. Each spectral component is identified by the center frequency and quantified by its power, ie, the area presented in absolute units (ms²) as well as in normalized units (nu). The normalization procedure consists of dividing the power of a given spectral component by the total variance diminished by the power of the very low frequency (below 0.03 Hz), when present, the result multiplied by 100. The use of normalized units facilitates comparison between spectra with large differences in total variance. Two major oscillatory components are detectable in the power spectrum of the RR variability: a low frequency (LF) component, index of sympathetic activity, and a high frequency (HF) component, synchronous with respiration, which reflects vagal modulation.

Four of the 22 patients (1 in the trained and 3 in the untrained group) could not be considered in the study of heart rate variability because of presence of artifacts in the Holter recording.

Exercise Training Program

The patients participated in a 4-week in-hospital training program of the endurance type. The exercise sessions consisted of calisthenics and stationary bicycle ergometry.

During the first week, the intensity of bicycle ergometry was adjusted to 75% of the anaerobic threshold measured with the analysis of gas exchange during the pretraining exercise stress test. Thereafter, the amount of physical activity was increased to 85% of the anaerobic threshold during the second and third week and to 95% during the last week.

Statistical Analysis

Data are presented as mean ± SE. Statistical analysis was performed by a one-way analysis of variance and Student's t test. Significance was accepted for values of p<0.05.

RESULTS

Exercise Stress Testing

At baseline, the 2 groups did not differ significantly in all ergometric parameters (Table 1).

In the untrained group, no difference has been observed between the first and second exercise stress test in the duration of exercise (14.6 ± 0.6 vs 14.7 ± 0.7 min) in heart rate at rest (75.4 ± 2.6 vs 74.3 ± 3.3 beats/min) and at the same work load (155.6 ± 4.6 vs 148 ± 5.4 beats/min). The double product at the same work load (28,520 ± 1,534 vs 27,800 ± 1,412 mm Hg × beats/min) and the anaerobic threshold (11.4 ± 0.5 vs 11.3 ± 0.6 min) were also unchanged. On the contrary, a significant increase in exercise duration was observed in the training group after the training period (13.7 ± 0.8 vs 17.0 ± 1.0 min, p<0.001) and the anaerobic threshold was equally delayed (9.5 ± 0.7 vs 12.0 ± 1.0 min, p<0.001).

Table 2 — Effect of Tilting on Heart Rate Variability in Untrained (UT) and Trained (T) Patients

<table>
<thead>
<tr>
<th>RR Interval, ms</th>
<th>RR Variance, ms²</th>
<th>Low Frequency Component</th>
<th>High Frequency Component</th>
<th>LF/HF Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest Tilt</td>
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<tr>
<td>UT</td>
<td>919 ± 58 768 ± 56</td>
<td>1,671 ± 511 625 ± 157</td>
<td>85 ± 3 83 ± 5 0.06 ± 0.01</td>
<td>0.08 ± 0.01</td>
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<tr>
<td>4 Weeks</td>
<td>945 ± 48 807 ± 45</td>
<td>1,494 ± 365 859 ± 256</td>
<td>80 ± 7 83 ± 4 0.07 ± 0.01</td>
<td>0.07 ± 0.01</td>
</tr>
<tr>
<td>8 Weeks</td>
<td>822 ± 45 704 ± 38</td>
<td>838 ± 209 527 ± 110</td>
<td>74 ± 4 79 ± 4 0.07 ± 0.01</td>
<td>0.08 ± 0.01</td>
</tr>
</tbody>
</table>

*p<0.05.

tp<0.01.
p<0.02). Resting heart rate was unchanged (83±4.2 vs 80±3.6 beats × min−1) while at the same work load a significant reduction was observed in heart rate (165±2.7 vs 152±3.1 beats × min−1, p<0.02) and double product (29,909±1,379 vs 27,120±1,330 mm Hg × beats × min−1, p<0.05).

**Spectral Analysis of Heart Rate Variability during Resting and Tiltting**

In resting condition in both groups, spectral analysis of heart rate variability showed a predominant LF component (85±3 nu UT, 74±4 nu T) and a smaller HF component (10±3 nu UT, 16±3 nu T) (Table 2). Tiltting was associated with a significant reduction in RR interval (768±56 ms UT, 704±38 ms T) while no change was observed in spectral profile, which remained characterized by a predominant LF (83±5 nu UT, 79±4 nu T) and a reduced HF (10±3 nu UT, 13±3 nu T) component.

At the second test, in resting condition, both groups showed a slight nonsignificant decrease in the LF component (80±7 vs 85±3 nu UT, 69±5 vs 74±4 nu T) and a similar increase in the HF component (14±5 vs 10±3 nu UT, 19±4 vs 16±3 nu T). As a consequence, little change was observed in the LF/HF ratio (14±5 vs 13±4 UT, 6±1 vs 6±1 T).

In untrained patients, head-up tilt did not produce any modification in spectral profile, while in trained patients, a significant increase in the LF component (84±3 vs 69±5 nu, p<0.01) (Fig 1) and a decrease in the HF component (7±1 vs 19±4 nu, p<0.05) was observed. As a result, the LF/HF ratio significantly increased (16±3 vs 6±1, p<0.01).

**DISCUSSION**

Our results support the concept of an impaired autonomic balance after myocardial infarction and do not show any spontaneous or time-related improvement between 4 and 8 weeks after the acute event. Four weeks of physical training did not induce any significant change of the autonomic balance in the resting state. When the system was placed under "stressful" condition, ie, when a reflex response was evoked by orthostatic stress, both the parasympathetic and the sympathetic limb showed a wider answer range in postmyocardial infarction patients submitted to physical training.

**Autonomic Nervous System and Myocardial Infarction**

Signs of enhanced sympathetic activity and reduced parasympathetic cardiac outflow have been found in most patients with acute myocardial infarction and do persist in the postinfarction period.

Several mechanisms may be responsible for the disordered autonomic function after MI. The destruction, secondary to MI, of vagal and sympathetic endings, may alter neural feedback to the higher centers, resulting in an increase in sympathetic and/or reduced vagal discharge. Alternatively, sustained activation of sympathetic cardiac afferent fibers, via an excitatory sympathetic reflex, may determine an increased sympathetic efferent activity. The postinfarction impairment of autonomic balance may not be totally related to structural damage to autonomic nerves. This derangement seems to be in part reversible, though conflict-

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21646/) Effect of short-term exercise training on low frequency spectral component of heart rate variability at rest (R) and after head-up tilt (T).

ing data do exist on the time course of recovery. Apart from the mechanisms responsible for the autonomic disturbances following myocardial infarction, the resulting increased sympathetic and/or depressed parasympathetic activity, by altering the electrical stability of the myocardium, may facilitate the expression of life-threatening arrhythmias and contribute significantly to sudden cardiac mortality. In dogs with healed anterior MI, a depressed baroreflex sensitivity and a reduced heart rate variability were associated with a greater risk for ventricular fibrillation. Similarly, recent clinical studies have addressed the prognostic significance of reduced cardiac vagal activity in post-MI patients.

Our data confirm the presence of an impaired autonomic function after myocardial infarction with signs of an increased sympathetic activity and a diminished vagal tone. In resting condition, spectral profile exhibited a predominant LF component and a reduced HF component as compared with normal subjects of similar age. As in previous observations, tilting did not induce any further increase in LF component, thus suggesting the evidence of a maximally activated sympathetic activity directed to the heart.

**Autonomic Nervous System and Exercise**

The data quoted above focus on the role of impaired autonomic balance on mortality after myocardial infarction. Therefore, it follows that interventions effective in favoring its return toward normal values would be beneficial on cardiac mortality in post-MI patients by diminishing the vulnerability to life-threatening arrhythmias and sudden cardiac death.

In post-MI patients, physical training as part of a comprehensive rehabilitation program has been shown to improve long-term prognosis. Adaptations in the autonomic nervous system have been considered to be responsible of some changes in cardiovascular parameters in trained patients, but data are still conflicting on the relative role of sympathetic and parasympathetic influence.

A readjustment of sympatho-vagal balance, with an increase in the gain of baroreceptor reflex mechanisms and the attendant enhancement of vagal modulation has been observed in mild hypertensive subjects after physical training. Moreover, in the same study, spectral analysis of RR variability revealed, in trained subjects, a significant decrease in LF and a marked increase in HF components, thus confirming the enhancement of vagal control of heart.
A reduction of the sympathetic outflow to the sinoatrial node has been suggested by a limited increase in plasma catecholamines during exercise after training in humans\(^a\) and by a reduced turnover of norepinephrine in the rat heart in response to exercise.\(^{27}\) On the other hand, a decrease in the adenylyl cyclase activity\(^a\) and a reduction in \(\beta_1\) - and \(\beta_2\)-adrenoreceptors observed in the hearts of trained rats\(^a\) may suggest a reduced responsiveness.

Evidence has been produced for an increase in cardiac parasympathetic tone,\(^{30-33}\) although other studies have failed to demonstrate consistent differences in vagal tone.\(^{34-36}\)

Several studies\(^{37-39}\) have demonstrated a significant decrease in sinus node rate after combined vagal and \(\beta\)-adrenergic blockade, thus suggesting an exercise-induced nonautonomic mechanism that lowers the "intrinsic" heart rate. It has been proposed that this reduction in "intrinsic" heart rate may be due to a mechanical effect on the pacemaker tissue imposed by cardiac hypertrophy or to an alteration of cardiac cell metabolism.

Along these concepts, it has been shown that exercise-induced increase in parasympathetic activity may exert a protective effect against life-threatening arrhythmias in susceptible dogs with a healed myocardial infarction.\(^{39}\) More recently, Posel et al.\(^{40}\) suggested that the underlying mechanism of the training-induced increase in ventricular fibrillation threshold in the ischemic heart may be the reduction in cyclic AMP content. This effect could be mediated by a decrease in myocardial sympathetic tone, an increase in parasympathetic tone, or both. The implications of augmented vagal activity are important, given the evidence that high vagal activity at onset of ischemia can prevent ventricular fibrillation in conscious animals with a healed myocardial infarction.\(^{40}\)

Our data confirm the improvement in cardiovascular performance after physical training. As expected, exercise duration was increased, together with a delayed appearance of the anaerobic threshold, heart rate and double product at the same work load were significantly reduced in trained as compared with untrained patients. No significant reduction was observed in resting heart rate and in resting spectral components of heart rate variability. Both in untrained and trained patients, spectral profile remained characterized by predominant LF and a smaller HF components, i.e., signs of sympathetic overactivity were not affected by a 4-week training period. It could be speculated that the duration and intensity of the training period should have been longer to induce significant changes in resting parameters. When a reflex response was evoked by orthostatic stress, significant differences were observed between trained and untrained patients. In untrained patients no significant differences in spectral components were found from resting to tilting. By contrast, in trained subjects, a significant improvement in the resting to tilting increase in LF component of heart rate variability associated with a significant decrease in HF component was observed. These data should be placed in context with our previous observation that, among post-MI patients, exercise training significantly increases baroreflex sensitivity.\(^{40,41}\)

Combining the previous and the present findings, it is possible to conclude that physical training can induce a significant increase in parasympathetic activity, documented by the increase in baroreflex sensitivity and a wider sympathetic reactivity, documented by the increased range of responses of the LF component of heart rate variability after orthostatic stress.

In conclusion, our data demonstrate that in post-MI patients after 4 weeks of physical training, although in the absence of significant change of the autonomic balance in resting condition, a restoration toward normal may be appreciated in the reflex activity of the system.

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