Effects of Long-Term Exercise Training on Autonomic Control in Myocardial Infarction Patients


Abstract—Autonomic dysfunction, including baroreceptor attenuation and sympathetic activation, has been reported in patients with myocardial infarction (MI) and has been associated with increased mortality. We tested the hypotheses that exercise training (ET) in post-MI patients would normalize arterial baroreflex sensitivity (BRS) and muscle sympathetic nerve activity (MSNA), and long-term ET would maintain the benefits in BRS and MSNA. Twenty-eight patients after 1 month of uncomplicated MI were randomly assigned to 2 groups, ET (MI-ET) and untrained. A normal control group was also studied. ET consisted of three 60-minute exercise sessions per week for 6 months. We evaluated MSNA (microneurography), blood pressure (automatic oscillometric method), heart rate (ECG), and spectral analysis of RR interval, systolic arterial pressure (SAP), and MSNA. Baroreflex gain of SAP-RR interval and SAP-MSNA were calculated using the α-index. At 3 to 5 days and 1 month after MI, MSNA and low-frequency SAP were significantly higher and BRS significantly lower in MI patients when compared with the normal control group. ET significantly decreased MSNA (bursts per 100 heartbeats) and the low-frequency component of SAP and significantly increased the low-frequency component of MSNA and BRS of the RR interval and MSNA. These changes were so marked that the differences between patients with MI and the normal control group were no longer observed after ET. MSNA and BRS in the MI-untrained group did not change from baseline over the same time period. ET normalizes BRS, low-frequency SAP, and MSNA in patients with MI. These improvements in autonomic control are maintained by long-term ET. These findings highlight the clinical importance of this nonpharmacological therapy based on ET in the long-term treatment of patients with MI. (Hypertension. 2011;58:1049-1056.) ● Online Data Supplement

Key Words: myocardial infarction ● sympathetic nerve activity ● exercise training ● autonomic control ● baroreflex control

Previous studies show that myocardial infarction (MI) is linked to increased sympathetic nervous activity1-2 and impaired arterial baroreflex sensitivity (BRS).3 These findings of autonomic dysfunction have been associated with increased mortality in patients after MI.4-10 La Rovere et al11 demonstrated that decreased BRS is associated with cardiac mortality risk. A follow-up of 61 months in uncomplicated post-MI patients with preserved left ventricular function showed that depressed BRS discriminated a subgroup at long-term high risk for cardiovascular mortality.10 Increased muscle sympathetic nerve activity (MSNA) is an independent predictor of poor prognosis in patients with chronic heart failure, including patients with chronic heart failure after MI.11 Thus, a therapeutic strategy targeted to the improvement in autonomic control in patients with MI represents an important clinical goal.

In patients with cardiovascular disease, studies have shown that physical exercise is an important strategy to improve autonomic function. Exercise training has been shown to decrease MSNA1-2 and improve BRS12-14 in patients with MI. It remains unknown whether the magnitude of change in autonomic control actually normalizes BRS and sympathetic nerve activity and whether these improvements can be sustained ≥7 months, time sufficient to observe the maintenance of the benefits caused by exercise training in patients with MI. In the present study, we described the changes in baroreflex control of heart rate and MSNA, in sympathetic nerve activity, and in heart rate and MSNA variability in exercise-trained patients with MI and how they compare with healthy individuals. In addition, we described the long-term effects of physical exercise in patients with MI.
Our hypotheses were that physical exercise would normalize BRS and sympathetic outflow, and the benefits of physical exercise on BRS and sympathetic nerve activity would maintain during a long-term exercise program.

Methods

Study Population
Following written informed consent, 28 patients with MI and 17 normal control subjects were included in this study. The first MI patient was randomly selected and the following patients were consecutively allocated in a 1:1 ratio to the exercise-trained (MI-ET) or untrained (MI-U) group. The calculation for the sample size took into consideration a power of 95%, with a 2-tailed type I error of 0.05, to detect a difference of 30% of reduction in MSNA after exercise training (the primary end point), assuming an SD of 16.6 bursts per 100 heartbeats, as observed in MI patients during the hospitalization phase after ischemic event.

The MI was diagnosed according to the European Society of Cardiology/American College of Cardiology proposal. In summary, the diagnosis included the typical rise and fall of biochemical markers of myocardial necrosis (troponin I and/or creatine kinase MB mass) with ≥1 of the following: (1) ischemic symptoms; (2) development of pathologic Q waves on the ECG; (3) ECG changes indicative of ischemia (ST segment elevation or depression); or (4) coronary artery intervention (eg, coronary angioplasty). All of the patients fulfilled the following criteria: (1) left ventricular ejection fraction ≥45%; (2) no previous acute coronary syndrome-related hospitalization ≥12 months before the study; (3) no significant coronary artery disease in arteries other than the infarct-related artery and no surgical revascularization during the hospitalization phase. None of the patients had a history of critical arrhythmia, congestive heart failure, clinical or echocardiographic evidence of valvular heart disease, renal insufficiency, or uncontrolled diabetes mellitus. Smoking habit was found in 1 patient in the trained group and 2 patients in the untrained group. This habit was unchanged during the study. The control group included healthy individuals by medical history and physical examination, resting ECG, and chest radiography, and none in the group were taking any medications. The study was approved by the human subject protection committee of the Heart Institute (InCor) and Clinical Hospital (University of Sao Paulo Medical School), and the participants gave their written informed consent.

Cardiopulmonary Exercise Testing
All of the patients were submitted to a cardiopulmonary exercise testing at 1, 3, and 7 months after MI. A detailed description of cardiopulmonary exercise testing method is available in the online Data Supplement, at http://hyper.ahajournals.org.

Exercise Training Program
After cardiopulmonary exercise testing, 1 month after MI, patients of the training group exercised under supervision at the Heart Institute. The 6-month training program consisted of three 60-minute exercise sessions per week. Each exercise session consisted of 5 minutes of stretching exercises, 40 minutes of cycling on an ergometer bicycle, 10 minutes of local strengthening exercises, and 5 minutes of cool down with stretching exercises. The exercise intensity was established by heart rate levels that corresponded with anaerobic threshold in the first 2 months. After this period, a new cardiopulmonary exercise test was performed to adjust the workload training and the aerobic exercise training, and the intensity was established by heart rate levels that corresponded with anaerobic threshold and ≤10% below the respiratory compensation point obtained in the cardiopulmonary exercise test in the last 4 months. The aerobic exercise training was monitored by ECG during the first 2 months. After hospital discharge, patients in the untrained MI group were advised to follow a home-base activity, which included mild walking. However, they were advised to avoid regular moderate exercise.

Measurements and Procedures

Muscle Sympathetic Nerve Activity
MSNA was directly measured from the peroneal nerve using the technique of microencephrography. A detailed description of the MSNA method is available in the online Data Supplement.

Spectral Analysis of RR Interval, Systolic Arterial Pressure, and MSNA
An automated computer program (Windaq) was used to process the ECG, blood pressure, and MSNA signals to extract the time series of heart rate (considering the RR interval [RRI]), systolic arterial pressure (SAP), and MSNA, respectively. A detailed description of the spectral analysis method is available in the online Data Supplement.

Baroreflex Control of RRI and MSNA
The sensitivity of baroreflex control of RRI was assessed as the baroreceptor gain of the SAP-RRI relationship by means of calculation of the α index (square root of the ratio between RRI spectral powers in the low-frequency [LF] regions). In addition, the sensitivity of baroreflex control of MSNA was assessed as the baroreceptor gain of the SAP-MSNA relationship by means of calculation of the α index (square root of the ratio between MSNA and SAP spectral powers in the LF regions). A detailed description of the baroreflex control of the RRI and MSNA method is available in the online Data Supplement.

Miscellaneous Measurements
Blood pressure was continuously and noninvasively measured by a finger photoplethysmography device (Finapres 2300, Ohmeda, Englewood, CO) on a beat-to-beat basis. Heart rate was monitored continuously through lead II of ECG. Respiratory rate was monitored with a piezoelctronic thoracic belt placed around the upper abdomen.

Experimental Protocol
All of the measurements were performed in a quiet, temperature-controlled (21°C) room at approximately the same time of day. The leg was positioned for microneurography, and an adequate nerve recording site was obtained. The subject then rested for 15 minutes with patients in the supine position. Baseline MSNA, blood pressure, heart rate, and respiratory frequency were recorded for 10 minutes during the hospitalization (3–5 days after MI) and at 1, 3, and 7 months after MI in both groups, MI-ET and MI-U. All of the variables were recorded on a computer sampling frequency of 500 Hz with a resolution of 16 bits and then analyzed in the program Windaq.

Statistical Analysis
The descriptive analyses of the data are presented as mean±SE. A detailed description of the statistical analysis is available in the online Data Supplement.

Results

Baseline Measures
All of the patients underwent percutaneous coronary intervention with success, during hospitalization. Physical, clinical, echocardiographic, and autonomic characteristics and medications between MI patients during hospitalization are shown in the Table. There were no differences between the MI-U and MI-ET groups regarding age, weight, height, body mass index, type of MI, levels of biochemical markers of myocardial necrosis, echocardiographic characteristics, medications, and autonomic characteristics. Echocardiographic characteristics showed no evidence of left ventricular dysfunction in patients with MI (Table). The physical characteristics of the normal control subjects were 47±2 years, 70.2±3.1 kg, 1.68±0.03 m, and 25±1 kg/m².
ET and Autonomic Control in MI Patients

Table. Physical, Clinical, and Echocardiographic Characteristics and Medications in Myocardial Infarction Patients During Hospitalization

<table>
<thead>
<tr>
<th>Characteristics of Population</th>
<th>MI-U (N=14)</th>
<th>MI-ET (N=14)</th>
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<td>Clinical characteristics</td>
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<tr>
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<td>LVEF, %</td>
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</table>

Values are mean±SE. MI-U indicates untrained myocardial infarction group; MI-ET, exercise training myocardial infarction group; BMI, body mass index; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non–ST-segment elevation myocardial infarction; CK-MB, creatine kinase MB; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-diastolic diameter; LVEDD, left ventricular end-systolic diameter; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LV mass, left ventricular mass; IVST, interventricular septal thickness; PWT, posterior wall thickness; ACE, angiotensin-converting enzyme; AT1, angiotensin receptor.

Effects of Exercise Training

In both the MI-ET and MI-U groups, no significantly changes were observed in body weight (80.0±3.4 versus 80.1±3.4 kg and 79.8±3.4 versus 82.1±3.6 kg, P=0.13, respectively) and body mass index (27±1 versus 27±1 kg/m² and 29±1 versus 29±1 kg/m², P=0.14, respectively). The effectiveness of physical exercise was observed at 7 months after MI (6 months of exercise training, Table S1, available in the online Data Supplement), when peak VO₂ was significantly increased in the MI-ET group compared with the baseline (20.6±1.0 versus 26.5±1.7 mL/kg per minute; P<0.001) and significantly higher than that observed in the MI-U group (26.5±1.7 versus 20.4±1.4 mL/kg per minute; P<0.001). During the same period, no significant changes in peak VO₂ were observed in MI-U patients. In both MI-ET and MI-U patients, heart rate significantly decreased 1 month after MI. This reduction of heart rate was maintained throughout the study. In both MI groups, systolic, mean, and diastolic arterial pressures were not significantly changed during the study (Table S1).

Examples of MSNA during study are shown in Figure 1. Two months of exercise training (3 months after MI) significantly reduced MSNA in bursts per minute (Figure 2A and 2C; P<0.001), bursts per 100 heartbeats (Figure 2B and 2D; P<0.001), and LF-SAP (Figure S1; P<0.05). This reduction in muscle and vascular sympathetic outflow was maintained throughout the exercise program, because MSNA in bursts per minute and bursts per 100 heartbeats and LF-SAP at 7 months after MI were lower in MI-ET compared with MI-U (P<0.001, P<0.001, and P=0.007, respectively). MSNA and LF-SAP were now indistinguishable from those of normal controls (Figure S2 and S3). In contrast, MSNA and LF-SAP remained elevated in MI-U. Further analysis showed that MSNA was inversely correlated with peak VO₂ (r=-0.45; P<0.001). LF-RRI, high-frequency (HF)-RRI, and LF/HF of RRI did not change during all of the experimental study in either group, MI-U or MI-ET (Table S1). Examples of sympathetic neurogram and power spectral of MSNA variability during study are shown in Figure 3. The LF spectral component of MSNA was significantly increased (P=0.02; Figure 4A) after exercise training in MI patients, whereas the HF spectral component of MSNA showed a tendency (P=0.09; Figure 4B) to decrease, and the LF/HF of MSNA showed a strong tendency (P=0.06; Figure 4C) to increase after exercise training in the MI-ET group. LF-MSNA, HF-MSNA, and LF/HF of MSNA did not change during all of the experimental protocol in the MI-U group.

With regard to baroreflex control of RRI, 2 months of exercise training (3 months after MI) significantly increased BRS in patients with MI (P<0.001). This effect of exercise training was maintained throughout the exercise program (Figure S4), and the difference observed from normal controls was no longer observed (Figure S5). Similarly, exercise training significantly increased baroreflex control of MSNA in patients with MI (P=0.02; Figure 4D). BRS of RRI and MSNA remained decreased in MI-U during all of the experimental protocol. Further analysis showed that baroreflex control of RRI was inversely correlated with MSNA and LF-SAP (r=-0.51, P=0.0001 and r=-0.54, P<0.001, respectively), and baroreflex control of MSNA was inversely correlated with the absolute levels of MSNA (r=-0.50; P<0.01).

Discussion

The present study was designed to provide insights into the magnitude of change in BRS and sympathetic nerve activity achieved by exercise training and the long-term effect of this nonpharmacological therapy in patients with MI. We found that, 3 months after MI, the levels of baroreflex control of RRI and LF-SAP and MSNA in the exercise training MI group were indistinguishable from those in healthy individuals. Moreover, these marked benefits in the autonomic control were maintained for 4 additional months of exercise training. The present study also showed that exercise training significantly increased the LF spectral component of MSNA and baroreflex control of MSNA in patients with MI. All
together, these findings highlight that 3 times per week of exercise markedly improves autonomic control in patients with MI, which contributes to the reduction in cardiovascular risk in these patients.

It is well understood that the first 6 months after MI is a critical period for arrhythmic death, which may be attributable to the sympathetic hyperactivity. Exercise training normalizes efferent sympathetic nerve activity during that period in patients with MI. More recently, we reported that MSNA >49 bursts per minute is an independent predictor of mortality in patients experiencing heart failure. In the present study, we found that exercise training normalized MSNA in MI-ET. In addition, previous reports show that BRS levels between 3.0 ms/mm Hg and 6.1 ms/mm Hg

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**Figure 1.** Time course of sympathetic neurograms and power spectral of systolic arterial pressure variability of an untrained (A) and an exercise-trained myocardial infarction patient (B). Note that 3 to 5 days and 1 month (1m) after myocardial infarction the muscle sympathetic nerve activity (MSNA) and the low frequency component of the systolic arterial pressure (LF-SAP) are markedly elevated on both myocardial infarction patients in relation to the normal control subject (NC). However, at 3 and 7 months after myocardial infarction (2 and 6 months after exercise training, respectively), MSNA and LF-SAP were expressively reduced in the exercise trained myocardial infarction patient and were similar to the normal control subject. In the untrained myocardial infarction patient, the MSNA and LF-SAP remained elevated during all of the time course studied.
increase the risk of cardiac mortality (relative risk of 2.1). Our study shows that 3 months after MI (2 months of exercise training), the baroreflex control of RRI increased from 6.0 ms/mm Hg to 15.6 ms/mm Hg in the MI-ET group. This benefit was even greater 7 months after MI (6 months of exercise training), when baroreflex control of RRI in MI-ET patients was 18.5 ms/mm Hg and similar to those observed in healthy controls (16.4 ms/mm Hg). Untrained post-MI patients did not present any improvement in the BRS parameter or MSNA along 7 months of follow-up, despite the same clinical management.

Other than reduction in averaged values of MSNA, exercise training changed the profile of the oscillatory pattern of MSNA. Sympathetic nerve activity presents the same very low–frequency, LF, and HF oscillatory components observed in other cardiovascular parameters like heart rate and arterial blood pressure. In addition, during physiological challenges, these spectral parameters of sympathetic activity presented similar responses to heart rate and arterial pressure variability. Our results showed a shift toward LF predominance in MI-ET patients. In contrast, MI-U patients maintained a spectral profile with a reduced (≈20% in normalized units) LF component. Previous reports have demonstrated a reduction in the LF component in MSNA in patients with congestive heart failure, which may have clinical implications. Thus, the increase in the LF component of MSNA may suggest a better prognostic in MI-ET patients. Furthermore, exercise training provoked an increase in the gain of the baroreflex control of MSNA, which paralleled with the improvement in the cardiac BRS. These findings reinforce the idea of a widespread effect of exercise training in different sites of baroreflex circuitry. The improvement of baroreflex control in these 2 different territories (heart and vessels) suggests that exercise training affects the afferent components or bulbar nuclei of the baroreflex pathway. In fact, Rondon et al demonstrated an improvement in aortic depressor nerve sensitivity after exercise training in rats with ischemia-induced heart failure.

The mechanisms by which exercise training markedly reduces MSNA remains little understood. However, the inverse association between the improvement in BRS and the reduction in vascular and MSNA suggests that arterial baroreflex control plays a role in this matter. This inverse association has been also reported in other studies involving patients with cardiovascular disease. Laterza et al found that exercise training improved BRS and decreased MSNA in never-treated hypertensive patients. Moreover, evidence in the infarct model in rats is consistent with the concept that the increase in BRS is attributed to enhancement in aortic depressor nerve discharge, which is suggestive of amelioration in blood vessel elasticity. It is well known that MI impairs not only reflexes from cardiac receptors but also activates sympathetic afferent fibers in the myocardium, which significantly contribute to sympathoexcitation. Exercise training significantly improves cardiopulmonary reflex control of renal sympathetic nerve activity in animal models.
of heart failure.\textsuperscript{25} Finally, we cannot rule out the possibility that exercise training has central nervous system effects as well. A series of studies by Zucker’s group\textsuperscript{26,27} have provided a lot of contribution regarding the central mechanisms by which exercise training reduces sympathetic outflow. They elegantly demonstrated that exercise training decreased mRNA and protein expression of angiotensin II type 1 receptors in the paraventricular nucleus of the hypothalamus and in the rostral ventrolateral medulla in exercise-trained heart failure rabbits.\textsuperscript{26} Furthermore, they reported that exercise training restored the number of neuronal NO synthase–positive neurons and their mRNA expression and protein levels in the paraventricular nucleus.\textsuperscript{27}

Another interesting piece of information in our study is the difference in time course between the improvement in autonomic control and functional capacity in MI-ET patients. Two months of exercise training (3 months after MI) significantly decreased LF-SAP and MSNA but produced no change in peak \( \dot{V}O_2 \). Functional capacity was improved only at 6 months of exercise training (7 months after MI). This mismatch in time course between changes in autonomic control and changes in functional capacity in patients with MI remains unexplained and deserves future investigation.

Although resting heart rate is a reliable marker of exercise training adaptation,\textsuperscript{28–30} this physiological parameter was unchanged in MI-ET patients. It is possible that administration of β-blockers obscured the expected reduction in resting heart rate induced by exercise. In fact, in previous studies from our laboratory in patients under β-blocker therapy drugs, we found no changes in resting heart rate after exercise training.\textsuperscript{31,32} In the present study, all of the patients (except 1) started β-blocker therapy immediately after MI, during the hospitalization phase, and the use of β-blockers was maintained throughout the experimental protocol.

Limitations
The use of β-blockers by MI patients decreased the resting heart rate, which might have altered the analysis of heart rate variability in our study. LF-RRI and HF-RRI were not different between exercise-trained MI patients and healthy individuals. Our exercise paradigm lasted 7 months. It is unknown whether the effects of exercise training on BRS and sympathetic outflow are maintained for a longer period, once exercise training is discontinued. Future studies are planned to address this question. Another possible limitation in the present investigation is that no other lifestyle changes were studied in the present investigation; however, the weight and body mass index were unchanged after intervention in both groups.

Perspectives
In our study, the compliance was very good. In fact, the attendance to exercise sessions was >92% in the present study. This is important information and should encourage the prescription of exercise training to patients with MI. The present study shows that our nonpharmacological strategy based on 3 times per week of exercise training for 6 months restores BRS and efferent sympathetic outflow in patients.
with MI, which renders exercise training a long-term protective effect in these patients.

In conclusion, exercise training restores BRS and sympathetic nerve activity in patients with MI. These marked effects of exercise training are maintained while exercise training continues. These findings highlight the clinical importance of this nonpharmacological therapy in patients with MI.

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Disclosures
None.

References


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ONLINE DATA SUPPLEMENT

Effects of Long-Term Exercise Training on Autonomic Control in Myocardial Infarction Patients

Daniel Godoy Martinez PhD¹, José Carlos Nicolau MD, PhD¹, Rony Lopes Lage MD¹, Edgar Toschi-Dias BS¹, Luciana Diniz Nagem Janot de Matos MD, PhD¹, Maria Janieire de Nazaré Nunes Alves MD, PhD¹, Ivani Credidio Trombeta Ph.D¹, Valdo José Dias da Silva MD, PhD², Holly R Middlekauff MD³, Carlos Eduardo Negrão PhD¹, Maria Urbana Pinto Brandão Rondon Ph.D¹, Maria Janieire de Nazaré Nunes Alves MD, PhD¹, Ivani Credidio Trombeta Ph.D¹, Valdo José Dias da Silva MD, PhD², Holly R Middlekauff MD³, Carlos Eduardo Negrão PhD¹, Maria Urbana Pinto Brandão Rondon Ph.D¹

¹Heart Institute (InCor), University of Sao Paulo Medical School, Brazil; ²School of Medicine, Federal University of the Triangulo Mineiro, Minas Gerais, Brazil, ³David Geffen School of Medicine at the University of California, Los Angeles, Division of Cardiology, ⁴School of Physical Education and Sports, University of Sao Paulo, Sao Paulo, Brazil

Short Title: ET and autonomic control in MI patients

Author for correspondence:
Maria Urbana Pinto Brandão Rondon, PhD
Escola de Educação Física e Esporte da Universidade de São Paulo
Av. Prof. Mello de Moraes, 65 - São Paulo - SP
CEP: 05508-030 - BRAZIL
Phone: (5511) 3091-3136 FAX: (5511) 3813-5921
E-mail: urbana@usp.br
Supplemental Methods

Cardiopulmonary Exercise Testing
All patients were submitted to a cardiopulmonary exercise testing on 1, 3 and 7 months after MI. Maximal exercise capacity was determined by means of a maximal progressive exercise test on an electromagnetically braked cycle ergometer (Medifit 400L, Medical Fitness Equipment, Maarn, Netherlands), with a ramp protocol with work rate increments of 10W, 15W or 20W every minute at 60 rpm until exhaustion. Oxygen uptake (VO₂) and carbon dioxide production were determined by means of gas exchange on a breath-by-breath basis in a computerized system (CAD/Net 2001, Medical Graphics Corporation, St. Paul, Minnesota). Peak VO₂ was defined as the maximum attained VO₂ at the end of the exercise period in which the subject could no longer maintain the cycle ergometer velocity at 60 rpm. This method is considered the gold standard for assessing patients’ exercise capacity. Anaerobic threshold was determined to occur at the breakpoint between the increase in the carbon dioxide output and VO₂ (V-slope) or the point at which the ventilator equivalent for oxygen and end-tidal oxygen partial pressure curves reached their respective minimum values and began to rise. Respiratory compensation was determined to occur at the point at which ventilatory equivalent for carbon dioxide was lowest before a systematic increase and when end-tidal carbon dioxide partial pressure reaches a maximum and begins to decrease. The reproducibility of the peak VO₂ measured at a different time interval in the same individual expressed as ml/kg/min in our laboratory is r =0.95.

Measurements and Procedures

Muscle Sympathetic Nerve Activity. MSNA was directly measured from the peroneal nerve using the technique of microneurography. Multiunit postganglionic muscle sympathetic nerve recordings were made using a tungsten microelectrode (tip diameter 5 to 15 μm). The signals were amplified by a factor of 50 000 to 100 000 and bandpassed filtered (700 to 2000 Hz). For recordings and analysis, nerve activity was rectified and integrated (time constant, 0.1 seconds) to obtain a mean voltage display of sympathetic nerve activity that was recorded on paper. Muscle sympathetic bursts were identified by visual inspection and data analysis was blinded to the investigator (M.U.R.). It was expressed as burst frequency (bursts per minute), and bursts incidence (bursts per 100 heart beats).

Spectral Analysis of RR interval, systolic arterial pressure and muscle sympathetic nerve activity. An automated computer program (Windaq) was used to process the ECG, blood pressure and MSNA signals to extract the time series of heart rate (considering the RR interval, RRI), systolic arterial pressure (SAP) and MSNA, respectively. Sympathetic bursts were identified by a careful inspection of the mean voltage neurogram. For each individual sympathetic burst, the computer program provided the time of occurrence and its amplitude (time x voltage area). In addition, time series of MSNA were provided through integration of the continuous MSNA signal, according to the following equation: \( MSNA_i = \frac{1}{t(i)} \int MSNA(t)dt \), where each integral was performed over the time window between two consecutive RRI delimiting the i-th cardiac cycle of period t(i). The MSNA time series were normalized by mean values of integrated area of bursts per cardiac cycle and expressed in arbitrary units (au). Spontaneous fluctuations of the RRI, SAP and MSNA time series were assessed in the frequency domain by means of autoregressive spectral analysis, reflecting autonomic cardiovascular modulation. Briefly, a modeling of the oscillatory
components present in the time series of RRI, SAP and MSNA was calculated based on the Levinson–Durbin recursion, with the order of the model chosen according to Akaike's criterion. This procedure allows an automatic quantification of the center frequency and power of each relevant oscillatory component present in the time series. RRI spectral powers were quantified in the low frequency band (LF, 0.04 to 0.15 Hz) representing cardiac sympathetic modulation predominance (LF-RRI) and the high-frequency band (HF, 0.15 to 0.4 Hz), synchronized with the breath, representing cardiac parasympathetic modulation (HF-RRI). SAP spectral powers were quantified in the LF band (LF-SAP, 0.4 to 0.15 Hz) representing vascular sympathetic modulation. In a subset of 7 MI-ET and 6 MI-U patients, MSNA spectral powers were quantified in the LF band (LF-MSNA, 0.4 to 0.15 Hz) and the HF band (HF-MSNA, 0.15 to 0.4 Hz), synchronized with the breath, to identify the oscillatory pattern of MSNA. The ratio of LF and HF (LF/HF) of RRI and MSNA was calculated to obtain the sympathe-vagal balance. The spectral analysis was blinded to the investigator (E.T).

**Baroreflex Control of RR Interval and Muscle Sympathetic Nerve Activity.** The sensitivity of baroreflex control of RRI was assessed as the baroreceptor gain of SAP-RRI relationship by means of calculation of $\alpha$-index (square root of the ratio between RRI and SAP spectral powers in the LF regions). In addition, the sensitivity of baroreflex control of MSNA was assessed as the baroreceptor gain of SAP-MSNA relationship by means of calculation of $\alpha$-index (square root of the ratio between MSNA and SAP spectral powers in the LF regions). The calculation of the $\alpha$-index requires the evaluation of coherence and phase shift between the RRI or MSNA and systolic arterial pressure time series. The bivariate autoregressive identification procedure was used to calculate the coherence ($k^2$) and phase shift ($\phi$) between the RRI or MSNA and SAP time series. The coherence function measures the degree of linear correlation between the oscillations at the same frequency in both variability signals, while the phase shift measures the time lag or lead between the signals. In the LF frequency range, the coherence between RRI and SAP is an expression of the baroreflex control of the heart rate while the coherence between MSNA and SAP is an expression of the baroreflex control of the MSNA. The $\alpha$-index was calculated in all cases since the coherence value was always significant ($k^2>0.5$) and the phase shift in radians was negative ($\phi<0$ radians, i.e., SAP changes precede RRI changes and SAP changes precede MSNA changes).

**Statistical Analysis**

The descriptive analyses of the data are presented as means ± SE. The comparisons of physical, clinical, echocardiographic and autonomic characteristics between MI-U and MI-ET groups were subjected to unpaired $t$-tests. The comparisons of the distribution of patients with ST-segment elevation myocardial infarction and non–ST-segment elevation myocardial infarction and, medications between groups were subjected to chi-square analysis. Two-way ANOVA with repeated measures was performed to test the differences between untrained and exercise-trained MI patients. One-way ANOVA was used to test the differences among untrained MI patients, exercise-trained MI patients and normal control group. When significance difference was found, Scheffé’s post-hoc comparison test was employed. Pearson correlation coefficient was used to evaluate the correlation between BRS and MSNA and LF-SAP, and MSNA and LF-SAP. Significant differences were assumed to be at $P<0.05$. 
Supplemental References


Supplemental Table

**Table S1.** Functional capacity, hemodynamic characteristics and spectral analysis of RR Interval in untrained and exercise training myocardial infarction groups during hospitalization and 1, 3 and 7 months after ischemic event.

<table>
<thead>
<tr>
<th>Characteristics of Population during study</th>
<th>MI-U (N=14)</th>
<th>MI-ET (N=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3-5 days</td>
<td>1 month</td>
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<tr>
<td><strong>Functional capacity and hemodynamic characteristics</strong></td>
<td></td>
<td></td>
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<tr>
<td>Peak VO$_2$ (mL/kg/min)</td>
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<td>20.4±1.6</td>
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<tr>
<td>SAP (mmHg)</td>
<td>117±6</td>
<td>125±5</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>82±4</td>
<td>85±2</td>
</tr>
<tr>
<td>DAP (mmHg)</td>
<td>65±3</td>
<td>66±2</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>61±2</td>
<td>55±2*</td>
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<tr>
<td><strong>Spectral Analysis of RR Interval</strong></td>
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<tr>
<td>Variance, ms$^2$</td>
<td>1388±275</td>
<td>2627±773</td>
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<tr>
<td>LF-RRI, ms$^2$</td>
<td>120±12</td>
<td>249±20</td>
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<tr>
<td>LF-RRI, nu</td>
<td>30±2</td>
<td>34±2</td>
</tr>
<tr>
<td>HF-RRI, ms$^2$</td>
<td>258±33</td>
<td>513±52</td>
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<td>HF-RRI, nu</td>
<td>56±2</td>
<td>63±1</td>
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<tr>
<td>LF/HF-RRI</td>
<td>0.90±0.12</td>
<td>0.67±0.06</td>
</tr>
</tbody>
</table>

Values are mean±SE. MI-U, untrained myocardial infarction group; MI-ET, exercise training myocardial infarction group; VO$_2$, oxygen consumption; SAP, systolic arterial pressure; MAP, mean arterial pressure; DAP, diastolic arterial pressure; HR, heart rate; RRI, RR interval; LF-RRI, low frequency band of RRI; HF-RRI, high frequency band of RRI; LF/HF-RRI, ratio of LF and HF of RRI. *= within-group comparisons vs. 3-5 days, P<0.001; †= between-group comparisons, P<0.001; ‡= within-group comparisons vs. 1 month, P<0.001.
Figure S1: Low frequency component of the systolic arterial pressure (LF-SAP) in untrained (MI-U) and exercise training myocardial infarction group (MI-ET). Note that LF-SAP significantly decreased at 3 (3m) and 7 (7m) months after myocardial infarction (2 and 6 months after exercise training, respectively) in MI-ET in relation to 3-5 days after myocardial infarction. No significantly changes of LF-SAP were observed in MI-U group during study protocol. * = difference vs. 3-5 days, P< 0.05; †= difference vs. MI-U, P<0.05.
Figure S2: Resting muscle sympathetic nerve activity (MSNA) expressed as burst incidence (bursts/100HB) in untrained (MI-U) and exercise training (MI-ET) myocardial infarction groups and normal control group (NC) at 3-5 days (Panel A), 1 month (1m, Panel B), 3 months (3m, Panel C) and 7 months (7m, Panel D) after myocardial infarction. Note that the MSNA was higher at 3-5 days and 1 month after myocardial infarction in MI-U and MI-ET groups when compared with NC group. However, the MSNA in the MI-ET group was similar to NC group and lower than MI-U group at 3 and 7 months after myocardial infarction (2 and 6 months after exercise training, respectively). HB= heart beats. ‡= difference vs. NC, P< 0.05; §= difference vs. MI-U, P<0.05.
Figure S3: Low frequency component of the systolic arterial pressure (LF-SAP) in untrained (MI-U) and exercise training (MI-ET) myocardial infarction groups and normal control group (NC) at 3-5 days (Panel A), 1 month (1m, Panel B), 3 months (3m, Panel C) and 7 months (7m, Panel D) after myocardial infarction. Note that the LF-SAP was higher at 3-5 days and 1 month after myocardial infarction in MI-U and MI-ET groups when compared with NC group. However, the LF-SAP in MI-ET group was similar to NC group and lower than MI-U group at 3 and 7 months after myocardial infarction (2 and 6 months after exercise training, respectively). ‡= difference vs. NC, P<0.05; §= difference vs. MI-U, P<0.05.
Figure S4: Baroreflex sensitivity (SAP-RRI) in untrained (MI-U) and exercise training myocardial infarction group (MI-ET). Note that the baroreflex gain significantly increased at 3 (3m) and 7 (7m) months after myocardial infarction (2 and 6 months after exercise training, respectively) in MI-ET in relation to 3-5 days after myocardial infarction. No significantly changes of baroreflex gain were observed in MI-U group during study protocol. * = difference vs. 3-5 days, P< 0.05; †= difference vs. MI-U, P<0.05.
Figure S5: Baroreflex sensitivity (SAP-RRI) in untrained (MI-U) and exercise training (MI-ET) myocardial infarction groups and normal control group (NC) at 3-5 days (Panel A), 1 month (1m, Panel B), 3 months (3m, Panel C) and 7 months (7m, Panel D) after myocardial infarction. Note that the baroreflex gain was depressed at 3-5 days and 1 month after myocardial infarction in MI-U and MI-ET groups when compared with NC group. However, the baroreflex gain in MI-ET group was similar to NC group and lower than MI-U group at 3 and 7 months after myocardial infarction (2 and 6 months after exercise training, respectively). ‡ = difference vs. NC, P < 0.05; § = difference vs. MI-U, P < 0.05.