Cardioprotective Properties of Aerobic and Resistance Training Against Myocardial Infarction

Authors
C. A. Barboza[1], G. I. H. Souza[1], J. C. M. F. Oliveira[1], L. M. Silva[1], C. T. Mostarda[2], P. M. M. Dourado[3], L. M. Oyama[4], F. S. Lira[5], M. C. Irigoyen[3], B. Rodrigues[6]

Affiliations
Affiliation addresses are listed at the end of the article

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- aerobic exercise training
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- myocardial infarction
- ventricular function
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Abstract

We evaluated the effects of aerobic and resistance exercise training on ventricular morphometry and function, physical capacity, autonomic function, as well as on ventricular inflammatory status in trained rats prior to myocardial infarction. Male Wistar rats were divided into the following groups: sedentary + *Sham*, sedentary + myocardial infarction, aerobic trained + myocardial infarction, and resistance trained + myocardial infarction. *Sham* and myocardial infarction were performed after training periods. In the days following the surgeries, evaluations were performed. Aerobic training prevents aerobic (to a greater extent) and resistance capacity impairments, ventricular dysfunction, baroreflex sensitivity and autonomic disorders (vagal tonus decrease and sympathetic tonus increase) triggered by myocardial infarction. Resistance training was able to prevent negative changes to aerobic and resistance capacity (to a greater extent) but not to ventricular dysfunction, and it prevented cardiovascular sympathetic increments. Additionally, both types of training reduced left ventricle inflammatory cytokine concentration. Our results suggest that aerobic and, for the first time, dynamic resistance training were able to reduce sympathetic tonus to the heart and vessels, as well as preventing the increase in pro-inflammatory cytokine concentrations in the left ventricle of trained groups. These data emphasizes the positive effects of aerobic and dynamic resistance training on the prevention of the negative changes triggered by myocardial infarction.

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Correspondence
Prof. Bruno Rodrigues
Faculty of Physical Education
University of Campinas (UNICAMP)
Av. Érico Veríssimo, 701
Cidade Universitária "Zeferino Vaz"
Barão Geraldo
CEP: 13.083-851
Campinas - SP, Brazil
Tel.: +55/19/35216 816
prof.brodrigues@gmail.com

Introduction

Despite advances in preventive medicine, cardiovascular disease remains the most prevalent condition worldwide, and coronary artery disease, followed myocardial infarction (MI), accounts for the majority of deaths worldwide [33]. MI is usually accompanied by autonomic imbalance associated with sympathetic nervous system hyperactivity. The latter plays a major role on cardiac remodeling (and consequently, in the progression to heart failure), on the increased incidence of arrhythmias, and often determines a poor prognosis for patients surviving MI [48].

The autonomic nervous system has been found to be a critical modulator of systemic and local inflammation [36]. Researchers have postulated that both increased sympathetic [34] and reduced parasympathetic [20] autonomic nervous system tonus have strong regulatory implications for the inflammatory process. The activation of inflammatory pathways, required for cardiac repair, may result in an imbalanced inflammatory response, thus becoming chronically involved in dilative and fibrotic remodeling after MI [33]. Prolonged or excessive induction of proinflammatory signaling is involved in the formation of collagen and matrix metalloproteinase, activation of profibrotic transforming growth factor beta (TGF-β) cascade, and integrin regulation, culminating in cardiac dysfunction [33,38].

It has been suggested that exercise training (ET) is an important non-pharmacological tool in the primary prevention and treatment of cardiovascular diseases, particularly MI [7,26,44]. After MI, ET has been associated with improvement of cardiac function [15,16,21], systemic and tissue inflammatory profile [1,41,42,44], as well as cardiac autonomic dysfunction [2,27,31]. On the other hand, a number of studies have been conducted in order to identify the mechanisms associated with a physically active lifestyle and the potential exercise-induced cardioprotection

against myocardial ischemia and reperfusion, and, to a lesser extent, against MI ([41] see for review).

In fact, a previous study by our group has suggested that previous aerobic ET was effective in improving aerobic capacity, left ventricular morphology and function in MI rats, possibly associated with attenuated cardiac autonomic dysfunction observed in trained rats [46]. However, although most studies have shown the cardioprotective role of aerobic ET prior to MI in rats, they have not indicated whether such effects could be extended to dynamic resistance ET. In the present work, we sought to advance our understanding about the role of aerobic ET performed prior to MI on left ventricle inflammatory parameters. Furthermore, to our knowledge, this is the first study evaluating the potential cardioprotective effects of resistance ET in rats. Thus, the aim of this study was to assess the effects of aerobic and resistance ET on ventricular morphometry and function, physical capacity, autonomic tonus and modulation, as well as on left ventricular inflammatory status in rats that trained prior to MI.

Methods

Experiments were performed using adult male Wistar rats (250–300 g) from the Animal House of the Sao Judas Tadeu University, São Paulo, Brazil. Rats were fed standard laboratory chow and water ad libitum. The animals were housed in collective polycarbonate cages in a temperature-controlled room (22 °C) with a 12 h dark-light cycle (light 07:00–19:00 h). The experimental protocol was approved by the Institution Animal Care and Use Committee of the Sao Judas Tadeu University, and this investigation was conducted in accordance with the journal's ethical standards in sport and exercise science research, 2014 update [18]. Rats were randomly assigned to 4 groups: sedentary control rats undergoing *Sham* surgery (C, n = 9), sedentary rats undergoing MI surgery (I, n = 13), aerobic trained (AT) rats undergoing MI surgery (ATI, n = 10), and resistance trained (RT) rats undergoing MI surgery (RTI, n = 10). The mortality rate was investigated during the protocol period in all animals (n = 42). The assessment began together with ET or following protocols. The potential influence of surgical and anesthetic procedures was excluded from this analysis.

Experimental design

The animals were trained or followed during 8 weeks prior to *Sham* or MI surgeries. Sedentary and trained groups underwent a maximal treadmill exercise test – and a maximal load test – at the beginning (for ET prescription), in the middle (for ET adjustments, data not show), at the end (to check the effectiveness of training protocols), of the protocol, and 2 days post-*Sham* or MI surgeries. During the first week after *Sham* or MI, the animals underwent echocardiography (one day after Sham/MI) and catheterization of the femoral arteries and veins for hemodynamic assessment, baroreflex sensitivity and autonomic tone evaluations. One day after all evaluations were performed, the animals were killed by decapitation in order to remove the left ventricle.

Aerobic exercise training

Sedentary and trained rats were adapted to the treadmill (10 min per day; 0.3 km/h) for 5 days. All animals underwent a maximal treadmill exercise test at the beginning of the protocol (initial evaluation, to determine aerobic capacity and aerobic ET prescription), after 4 weeks (data not show, for adjustments in running intensity), after aerobic ET protocol (final evaluation, to determine aerobic capacity and enable comparisons), and 2 days after *Sham* or MI surgeries (to determine aerobic capacity and enable comparisons). The maximal treadmill exercise test were performed on a ramp treadmill and consisted of exercises with 3 m/min increments every 3 min until the animals were no longer able to run. Our group has previously demonstrated that the maximal treadmill exercise test can detect differences in aerobic performance, since the maximal running speed achieved in the test presents a good correlation with the maximum oxygen consumption [43]. Aerobic ET was performed on a motorized treadmill at low-moderate intensity (50–70% maximal running speed) for 1 h a day, 5 days a week for 8 weeks. Based on maximal treadmill exercise tests, training speeds ranged from 0.3 to 1.5 Km/h during the 8 weeks of training [45].

Resistance exercise training

All groups underwent a maximal load test protocol and resistance ET performed on a ladder adapted for rats. The ladder had 54 vertical steps with a distance of 0.5 cm between each rung and a small rat cage at the top, which was covered with a cloth to promote a dark environment for animal rest between the climbs. The weights used as load were mounted with fishing weights, and were attached to the base of the rat tail. The test consisted of an initial load of 75% of body weight, which was progressively increased by an additional 15% of body weight during the subsequent climbs, as previously described. The animals were gradually adapted to climbing for 5 consecutive days before the maximal load test [17,47]. Maximal load test at the beginning of the protocol (initial evaluation) was used to determine load capacity and resistance ET intensity prescription; after 4 weeks (data not show, for adjustments in training intensity), after ET protocol (final evaluation, to determine load capacity and comparisons), and 2 days after *Sham* or MI surgeries (to determine load capacity and comparisons).

The resistance ET prescription was based on the normalized value of maximal load for each rat, and was adjusted each week to the animal's body weight. Resistance ET protocol was performed over 8 weeks, 5 days a week, with 15–20 climbing per session, with a 1-min rest between each climbing. The intensity of training was low to moderate (40–60% of the normalized maximum load test) [17,47], as recommended for patients with cardiovascular disease [53]. Each climb had an average duration of 5 s, and the average of articular movements per climb was 8–12, due to the fact that while climbing animals tend to skip ladder rungs. For more details, see Sanches et al. [47].

Myocardial infarction surgery

Anaesthetized rats (80 mg/kg ketamine and 12 mg/kg xylazine, i.p.) underwent surgical occlusion of the left coronary artery, which resulted in MI, as previously described [2,17,21,44,46]. Briefly, after intubation, animals were positive-pressure ventilated with room air at 2.5 mL, 65 strokes/min with a pressure-cycled rodent ventilator (Harvard Apparatus, Model 683, Holliston, MA, USA). For induction of MI, a 2-cm left lateral thoracotomy was performed in the third intercostal space, and the left anterior descending coronary artery was occluded with a nylon (6.0) suture at approximately 1 mm from its origin below the tip of the left atrium. The C animals underwent the same

procedures, except that myocardial ischemia was not induced. The chest was closed with a silk suture.

Left ventricular echocardiographic evaluation

One day after *Sham* or MI surgeries, echocardiographic evaluations were performed by a blinded observer, under the guidelines of the American Society of Echocardiography. Rats were anaesthetized (80 mg/kg ketamine and 12 mg/kg xylazine, i.p.), and images were obtained with a 10–14 mHz linear transducer in a SEQUOIA 512 (Acuson Corporation, MountainView, CA, USA) for measurements of parameters: left ventricular mass (LVmass); left ventricular end-diameter during diastole (LVDD); relative wall thickness (RWT); ejection fraction (EF); E wave A wave ratio (E/A); myocardial performance index (MPI), as described in detail elsewhere [2, 45].

The MI area was determined by taking into account the movement of the left ventricular walls during the initial and final echocardiographic evaluations undertaken by a blinded observer. MI was defined by echocardiography as any segmental wall motion abnormality such as hypokinesis, akinesis and dyskinesis, as previously described [2, 45]. Our group has previously demonstrated strong correlations between the MI area assessed by echocardiogram and post mortem histological analysis [21], thus showing that this is a valid method to estimate MI area in rats.

Hemodynamic, baroreflex sensitivity and autonomic tonus assessments

One day after the final exercise tests, 2 catheters filled with 0.06 mL saline were implanted in the femoral artery and vein (PE-10) while the animals were anesthetized (80 mg/kg ketamine and 12 mg/kg xylazine, i.p.) for direct measurements of arterial pressure (AP) and drug administration, respectively. Rats were studied one day after catheter placement; the rats were conscious and allowed to move freely during the experiments. The arterial cannula was connected to a strain-gauge transducer (Blood Pressure XDCR; Kent Scientific, Torrington, CT, USA), and AP signals were recorded over a 30-min period by a microcomputer equipped with an analog-to-digital converter board (WinDaq, 2 kHz, DATAQ, Springfield, OH, USA). The recorded data were analyzed on a beat-to-beat basis to quantify changes in mean AP and heart rate (HR) [2, 45].

Sequential bolus injections of increasing doses of phenylephrine (0.25–32 µg/kg) and sodium nitroprusside (0.05–1.6 µg/kg) were given to induce at least 4 pressure responses (for each drug) ranging from 5 to 40 mmHg. A 3- to 5-min interval between doses was necessary for AP to return to baseline. Peak increases or decreases in mean AP after phenylephrine or sodium nitroprusside injection and the corresponding peak reflex changes in HR were recorded for each dose of the drug. Baroreflex sensitivity was evaluated by a mean index, calculated by the ratio between changes in HR to the changes in mean AP, allowing a separate analysis of bradycardic and tachycardic responses. The mean index was expressed as bpm/mmHg, as described elsewhere [2, 45].

After baroreflex sensitivity assessment, AP and HR were continuously recorded at basal state and after methylatropine (3 mg/kg, i.v.) injection (0.2 mL). Because HR response to the drug reaches its peak within 3–5 min, this time interval was allowed to elapse before HR measurement. Atenolol (8 mg/kg, i.v.) was injected (0.2 mL) 10 min after methylatropine, and the response was again evaluated after simultaneous blockade with atenolol and methylatropine. On the subsequent day, the sequence of injections was inverted (first atenolol and then methylatropine). The intrinsic heart rate (IHR) was evaluated after simultaneous blockade with atenolol and methylatropine. Sympathetic tonus was determined as the difference between maximum HR after methylatropine injection and IHR. Vagal tonus was obtained by the difference between the lowest HR after atenolol injection and IHR [32].

Cardiovascular autonomic modulation

The overall variability of pulse interval (PI) and systolic AP (SAP) in the time domain was assessed by the standard deviation (SD) and variance of the time series. Fluctuations in PI and SAP were further assessed in the frequency domain by means of autoregressive spectral estimation. The theoretical and analytical procedures for autoregressive modelling of oscillatory components have been previously described [17, 25]. Briefly, the PI and SAP series derived from each recording were divided into 300-beat segments with a 50 % overlap. The spectra of each segment were calculated via the Levinson-Durbin recursion, and the order of the model was chosen according to Akaike's criterion, with the oscillatory components quantified in low frequency (LF; 0.2–0.6 Hz) and high-frequency (HF; 0.6–3.0 Hz) ranges. The normalized units were obtained by calculating the power of LF and HF correlating each to the total power, after subtracting the power of the very LF component (frequencies < 0.2 Hz).

Cytokines concentration assessed by ELISA

Frozen left ventricle tissues were homogenized in RIPA buffer (0.625 % Nonidet P-40, 0.625 % sodium deoxycholate, 6.25 mM sodium phosphate, and 1 mM ethylenediaminetetraacetic acid at pH 7.4) containing 10 µg/mL of a protease inhibitor cocktail (Sigma-Aldrich, St. Louis, MO, USA). Homogenates were centrifuged at 12 000 g for 10 min at 4 °C, the supernatant was saved, and protein concentration was determined using the Bradford assay (Bio-Rad, Hercules, CA, USA) with bovine serum albumin as a reference. Quantitative assessment of tumor necrosis factor alpha (TNF-α), interferon gama (IFN-γ), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and interleukin-10 (IL-10) proteins was carried out by ELISA (DuoSet ELISA, R&D Systems, Minneapolis, MN, USA). The sensitivity of the assays was found to be 5.0 pg/mL in the range of 31.2–2 000 pg/mL. All samples were run as duplicates, the mean value was reported, and the results were normalized by left ventricle total protein extracted using the Bradford method [45].

Statistical analysis

Statistical analysis was performed with SPSS software (Version 20.0 for Windows; SPSS Inc., Chicago, USA). Data are reported as mean ± SEM. After confirming that all continuous variables were normally distributed using the Kolmogorov-Smirnov test, statistical differences between the groups were obtained by two-way ANOVA, followed by the Bonferroni post-test. Statistical differences between the data measured over time were assessed using repeated-measures ANOVA. Pearson's correlation was used to study the association between sympathetic tonus and LF band of PI with TNF-α levels in the left ventricle. Survival analysis was estimated by the Kaplan-Meier method and compared by the log-rank (Mantel-Cox) test. All tests were 2 sided and the significance level was established at $P < 0.05$.

Results

Mortality rate

During ET protocols or following periods, no deaths were registered. After MI or *Sham* surgery, the I group (3 deaths among 13 I rats, 23%) displayed increased mortality rate when compared to the C group (no deaths). Previous ET, regardless of type (either aerobic or resistance), was able to reduce mortality rate in ATI (1 death among 10 ATI rats, 10%) and RTI (1 death among 10 RTI rats, 10%) animals.

Body weight and physical capacity

Body weight was similar among studied groups at the beginning of the protocol (~279±10 g). At the end of the protocol, the experimental groups showed increased body weight when compared to their initial values. However, at the final evaluation, both ATI and RTI groups displayed decreased body weight when compared to C and I. Additionally, this variable was reduced in the RTI group when compared to ATI group. After Sham/MI surgeries, although a discrete loss of body weight has been observed in I and ATI groups, body weight remained higher when compared to the initial evaluation, while ATI was decreased when compared to C and I group. It should be stressed that after MI, the RTI group remained with similar body weight when compared to the initial evaluation and presented decreased body weight when compared to C, I and ATI groups.

Soleus muscle weight was increased in RTI (0.18±0.02 g) group when compared to I (0.11±0.01 g); however, no changes were observed between other experimental groups (C: 0.13±0.02; ATI: 0.14±0.01 g).

Maximal treadmill exercise test and maximal load test results are shown in **Table 1**. Initial values of maximal treadmill exercise test and load test were similar among the groups. I rats presented reduced values at the end of the maximal treadmill exercise test when compared to the C, ATI and RTI rats. On the other hand, RTI group demonstrated a decrease in this variable when compared to the ATI group. After MI surgery, the infarcted groups (I, ATI and RTI) displayed decreased aerobic capacity when compared to their final evaluations and to the C group. However, resistance and aerobic ET were able to prevent such a decrease. It should be noted that the ATI group preserved a higher aerobic capacity when compared to RTI group.

Regarding maximal load test, the experimental groups displayed increased values at the final evaluation when compared to the initial evaluation. These values were even higher for RTI rats when compared to C, I and ATI animals. After MI surgery, maximal load test values were reduced in I rats when compared to their final evaluation and to C rats, while this impairment was not observed in ATI rats. Although this parameter was reduced in the RTI animals after MI, the values were increased when compared to all experimental groups.

Ventricular function

MI area values, measured by echocardiogram, were not changed by exercise training protocols. Left ventricle morphometric evaluations (**Table 2**) demonstrated that ventricular mass and relative wall thickness were increased by aerobic (ATI group) and resistance ET (RTI group), when compared to C and I animals. Furthermore, RTI animals displayed an additional increase in these variables when compared to ATI animals. Similarly, ejection fraction and E/A ratio impairment were prevented by aerobic ET, as these values were better in ATI group than in RTI group. In contrast, both aerobic and resistance ET prevented the increase in myocardial performance index, as observed in ATI and RTI groups (**Table 2**).

Hemodynamic and autonomic evaluations

As shown in **Table 3**, systolic, diastolic and mean arterial pressures were not changed by ET protocols. However, heart rate values were increased in I and RTI animals, when compared to C and ATI animals, respectively. Baroreflex sensitivity, evaluated by bradycardic and tachycardic responses evoked by arterial

	C	I	ATI	RTI
BW initial (g)	283±7	279±3	288±5	265±7
BW final (g)	425±9#	417±8#	367±7#*†	310±12#*†‡
BW post *Sham*/MI (g)	429±8#	405±7#	364±9#*†	294±8*†‡
MET initial (Km/h)	1.42±0.11	1.40±0.05	1.45±0.06	1.43±0.04
MET final (Km/h)	1.63±0.06	1.60±0.05	2.61±0.05#*†	2.05±0.05#*†‡
MET post *Sham*/MI (Km/h)	1.51±0.04	0.88±0.04¥*	1.25±0.04¥*†	1.02±0.07¥*†‡
MLT initial (g)	290±25	275±15	279±20	269±24
MLT final (g)	350±12#	358±10#	355±15#	415±9#*†‡
MLT post *Sham*/MI (g)	335±19	305±12¥*	337±11#†	385±9#¥*†‡

Values are expressed as mean±SEM. Repeated measurements ANOVA and Bonferroni post-test. MI – myocardial infarction. # P<0.05 vs. Initial in the same group; ¥ P<0.05 vs. Final in same group; * P<0.05 vs. C; † P<0.05 vs. I; ‡ P<0.05 vs. ATI

Table 1 Time course of body weight, maximal exercise test (MET) and absolute values of maximal load test (MLT) in the control animals (C, n=9), sedentary animals submitted to MI (I, n=10), aerobic trained animals submitted to MI (ATI, n=9), and resistance trained animals submitted to MI (RTI, n=9).

	C	I	ATI	RTI
MI area (%)	–	41±5	38±7	44±8
LV mass (g)	1.13±0.03	1.17±0.05	1.60±0.11*†	1.95±0.08*†‡
LVDD (cm)	0.75±0.01	0.77±0.04	0.74±0.03	0.72±0.02
RWT	0.38±0.03	0.32±0.01*	0.55±0.03*†	0.69±0.04*†‡
EF (%)	72.5±0.7	39.8±0.9*	55.5±0.5*†	44.2±1.1*‡
E/A	1.65±0.15	2.70±0.11*	1.78±0.13†	2.32±0.22*†‡
MPI	0.35±0.02	0.51±0.06*	0.21±0.03*†	0.26±0.04*†

Values are expressed as mean±SEM. Two-way ANOVA and Bonferroni post-test. MI – myocardial infarction; LV mass – left ventricular mass; LVDD – left ventricular diastolic diameter; RWT – relative wall thickness; EF – ejection fraction; E/A – E and A ratio; MPI – myocardial performance index. * P<0.05 vs. C; † P<0.05 vs. I; ‡ P<0.05 vs. ATI

Table 2 Echocardiographic measurements of left ventricular morphometry and function in the control animals (C, n=9), sedentary animals submitted to MI (I, n=10), aerobic trained animals submitted to MI (ATI, n=9), and resistance trained animals submitted to MI (RTI, n=9).

	C	I	ATI	RTI
SAP (mmHg)	120 ± 4	118 ± 7	122 ± 5	125 ± 3
DAP (mmHg)	83 ± 4	86 ± 5	88 ± 8	87 ± 6
MAP (mmHg)	95 ± 3	90 ± 6	96 ± 6	100 ± 7
HR (bpm)	322 ± 6	334 ± 9 *	329 ± 4	340 ± 8 *‡
TR (bpm/mmHg)	3.31 ± 0.24	1.59 ± 0.12 *	2.89 ± 0.05†	−1.89 ± 0.15 *‡
BR (bpm/mmHg)	−2.03 ± 0.12	−0.59 ± 0.02 *	−2.01 ± 0.07†	−0.90 ± 0.09 *‡

Values are expressed as mean ± SEM. Two-way ANOVA and Bonferroni post-test. SAP – systolic arterial pressure; DAP – diastolic arterial pressure; MAP – mean arterial pressure; HR – heart rate; TR – tachycardic responses; BR – bradycardic responses. * P < 0.05 vs. C; † P < 0.05 vs. I; ‡ P < 0.05 vs. ATI

Table 3 Hemodynamic and baroreflex sensitivity values in the control animals (C, n = 9), sedentary animals submitted to MI (I, n = 10), aerobic trained animals submitted to MI (ATI, n = 9), and resistance trained animals submitted to MI (RTI, n = 9).

pressure rises and falls, was impaired in I group. Aerobic ET (ATI group) was able to prevent this dysfunction, but resistance ET (RTI group) was not.

After MI, the I group displayed increased values of sympathetic tonus and intrinsic heart rate, as well as reduced values of vagal tonus when compared to the C group (**Fig. 1**). Aerobic and resistance ET prevented sympathetic tonus and intrinsic heart rate increase in both ATI and RTI groups. In contrast, only the ATI group prevented decreases in vagal tonus, while such effect was not observed in the RTI group (**Fig. 1**).

Cardiac autonomic modulation parameters, evaluated by pulse interval variability in time and frequency domains, are shown in **Table 4**. Standard deviation of pulse interval variability was increased in ATI group when compared to I group. MI promoted a reduction of pulse interval variance, RMSSD, LF band, HF band and LF/HF, as observed in I animals. However, aerobic and resistance ET were able to prevent such reductions. It should be noted that RMSSD and HF band, both indicators of parasympathetic modulation, were reduced in RTI animals when compared to ATI animals.

Vascular autonomic modulation parameters, evaluated by SAP variability, are presented in **Fig. 2**. SAP variance values were reduced in ATI and RTI groups when compared to I group (**Fig. 2a**). LF band of SAP, an indicator of vascular sympathetic modulation, was increased in I animals when compared to C animals. However, both types of ET were able to prevent such increase (**Fig. 2b**). Spontaneously baroreflex modulation, as evaluated by alpha index, was reduced in I rats when compared to C (**Fig. 2c**). Nevertheless, only aerobic ET was able to prevent this reduction.

Cytokines concentration of left ventricle

As shown in **Fig. 3**, after MI the I group presented increased expression of pro-inflammatory cytokines TNF-α (**Fig. 3a**), IFN-γ (**Fig. 3b**), IL-1β (**Fig. 3c**), IL-6 (**Fig. 3d**), as well as increased anti-inflammatory cytokine IL-10 (**Fig. 3e**), when compared to the C group. However, these results were not observed in both aerobic and resistance ET rats. IL-10/TNF-α was increased only in I group when compared to C group (**Fig. 3f**). Additionally, the prevention of sympathetic tonus increase (r = 0.74; P = 0.001) and LF band of pulse interval variability decrease (r = −0.76; P < 0.001) were correlated with the reduction of ventricular concentration of TNF-α in the experimental groups.

Discussion

The main results and new findings of this study can be thus summarized: 1) prior to MI, aerobic ET prevents additional aerobic and resistance capacity impairments, left ventricular dysfunction, baroreflex sensitivity, and cardiovascular sympathetic increase, as well as the cardiac parasympathetic decrease evoked by MI. 2) Prior to MI, resistance ET was able to prevent additional negative changes on the aerobic and strength capacity, myocardial performance index increase, and the cardiovascular sympathetic increments initiated by MI. Additionally, 3) both types of ET triggered cardioprotective mechanisms, possibly associated with the prevention of cardiac sympathetic overactivation, along with reduced concentration of inflammatory cytokines in the left ventricle of rats undergoing training prior to MI.

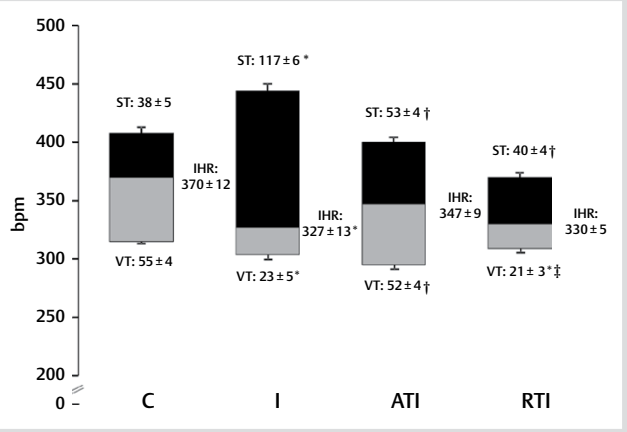

Fig. 1 Intrinsic heart rate (IHR), sympathetic (ST) and vagal (VT) tonus in control animals (C, n = 9), sedentary animals submitted to MI (I, n = 10), aerobic trained animals submitted to MI (ATI, n = 9), and resistance trained animals submitted to MI (RTI, n = 9). Two-way ANOVA and Bonferroni post-test. * P < 0.05 vs. C; † P < 0.05 vs. I; ‡ P < 0.05 vs. ATI.

Studies have indicated that ET promotes cardioprotection against myocardial ischemia through 2 stages: the first seems to occur soon after 0.5 h of an ET session, and has been associated with the production of mitochondrial antioxidants [19,54]. However, this phase is short and does not last more than 3 h after exercise. The late phase of cardioprotection by exercise is reached after 24 h of the session; it may continue over 9 days [23,41], and this long lasting effect is the focus of our investigation. In this study, besides investigating the cardioprotective role of aerobic exercise, we attempted to shed light on the possible candidate mechanisms underlying cardioprotection through resistance ET.

Cardiovascular dysfunction

In the present study, we showed that aerobic ET was able to prevent negative changes in physical capacity, left ventricular morphology, and systolic and diastolic function in rats undergoing MI, thus corroborating previous findings of our group [46]. Dayan et al. [8] have demonstrated similar results; in their study, a short-term ET (3 weeks of aerobic swimming), was able to pre-

	C	I	ATI	RTI
SD (bpm)	10.4±0.6	8.4±0.7	11.4±0.9†	9.7±0.7
Variance (ms^2)	114.7±14.1	27.4±2.9*	112.9±10.7†	111.8±11.0†
RMSSD (ms^2)	7.1±0.4	3.9±0.3*	9.0±0.8†	6.5±0.7†‡
LF (ms)	6.1±0.7	0.7±0.2*	5.9±0.6†	5.4±0.8†
LF (%)	25.9±1.9	13.7±1.8*	26.1±2.1†	21.6±2.9
HF (ms)	14.8±0.9	4.1±0.6*	17.9±1.1†	11.5±2.7†‡
HF (%)	74.0±3.1	87.5±2.2*	76.3±3.9	78.3±3.9
LF/HF	0.40±0.07	0.17±0.03*	0.36±0.05†	0.43±0.04†

Values are expressed as mean±SEM. Two-way ANOVA and Bonferroni post-test. SD – standard deviation of the PI variability; RMSSD – root-mean square of differences of successive RR intervals; LF – low frequency band; HF – high frequency band; LF/HF – autonomic balance. * P<0.05 vs. C; † P<0.05 vs. I; ‡ P<0.05 vs. ATI

Table 4 Pulse interval (PI) variability in time and frequency domains in the control animals (C, n=9), sedentary animals submitted to MI (I, n=10), aerobic trained animals submitted to MI (ATI, n=9), and resistance trained animals submitted to MI (RTI, n=9).

vent ventricular dysfunction, despite unchanged cardiac dimensions, suggesting that this period of training was sufficient to promote cardiac protection. Also, Bozi et al. [4] have previously shown that ET on a treadmill attenuated physical capacity decline, cardiac dysfunction and structural negative changes promoted by MI. On the other hand, Veiga et al. [52] have not observed any significant changes in trained hearts of female rats undergoing swimming training prior to MI.

Regarding MI area, Freimann et al. [14] have shown that after 7 weeks of swimming ET, trained animals displayed reduction of MI scar when compared to sedentary ones. The researchers found an increased arteriolar density in the hearts of animals undergoing ET, suggesting that an enhanced arteriogenesis in this group may have accounted for ET-induced cardioprotection. Similarly, when mice were exposed to voluntary wheel running 2 weeks before MI, apoptosis and collagen content were reduced when compared to with sedentary animals [9]. In the present study, our ET protocols failed to reduce MI area in experimental animals. It is possible that the differences between our results and literature findings are due to the type of training performed (swimming or voluntary wheel running vs. aerobic (treadmill) or resistance ET), animals type (mice vs. rats), time of evaluation after MI, as well as the MI area analysis carried out (histological methods vs. echocardiographic evaluation). Although we did not perform histological analysis of MI area, aerobic ET training prevented cardiac dysfunction in trained rats before MI. This finding suggests that previous aerobic ET may positively affect remaining myocardium, thus promoting a protected cardiac phenotype of the exercising animals, as suggested by Freimann et al. [13].

In this sense, several underlying mechanisms have been proposed for aerobic exercise cardioprotection: delta opioid receptor [30], increased calcitonin gene-related peptide in the blood and heart [50], endothelial nitric oxide synthase uncoupling associated with the improved myocardial antioxidant capacity [12], as well as increased glycolytic flux, changes of heat shock proteins, myocardial cyclooxygenase-2 activity, endoplasmic reticulum stress proteins, and sarcolemmal and/or mitochondrial ATP-sensitive potassium channels function [41].

Although many studies have addressed their efforts towards the understanding of the cardioprotective mechanisms associated with aerobic ET, we also evaluated the possible cardioprotective effects of resistance ET.

In the present investigation, we showed that dynamic resistance ET, performed prior to MI, was able to prevent aerobic and resistance capacity reduction and myocardial performance index increase – an index that represents cardiovascular global function – as well as intrinsic heart rate decrease in resistance ET animals. Chicco et al. [6] have reported that resistance ET attenu-

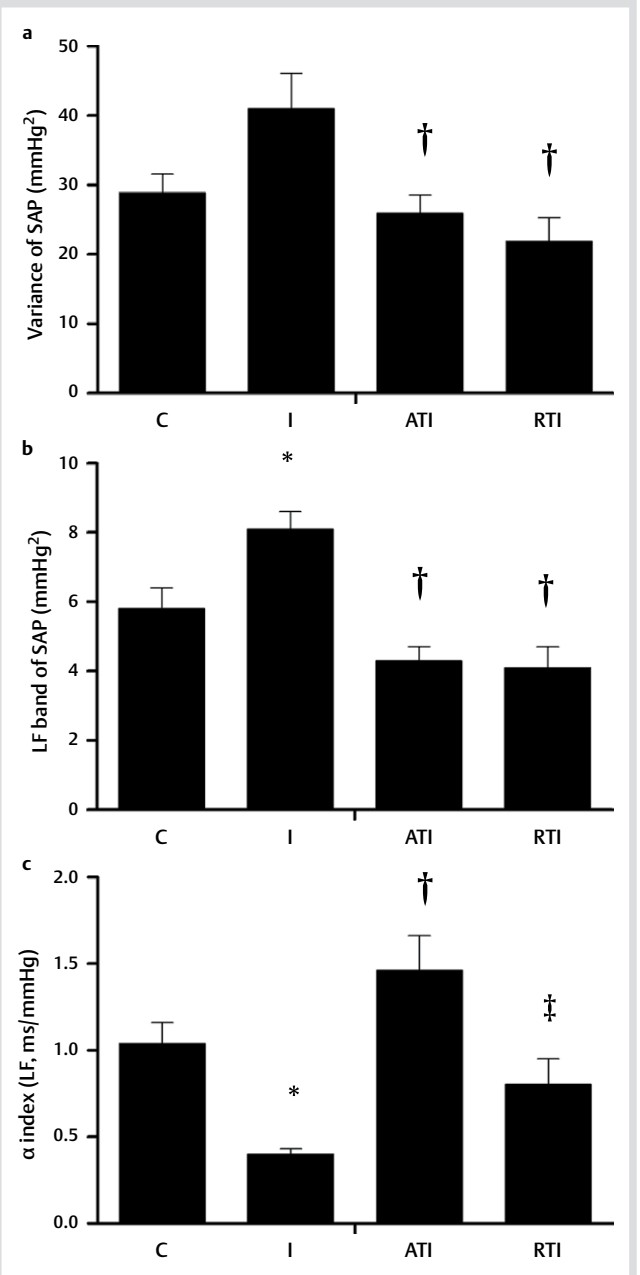

Fig. 2 **a** Variance of systolic arterial pressure, **b** low frequency band (LF) of systolic arterial pressure, and **c** alpha index in control animals (C, n=9), sedentary animals submitted to MI (I, n=10), aerobic trained animals submitted to MI (ATI, n=9), and resistance trained animals submitted to MI (RTI, n=9). Two-way ANOVA and Bonferroni post-test. * P<0.05 vs. C; † P<0.05 vs. I; ‡ P<0.05 vs. ATI.

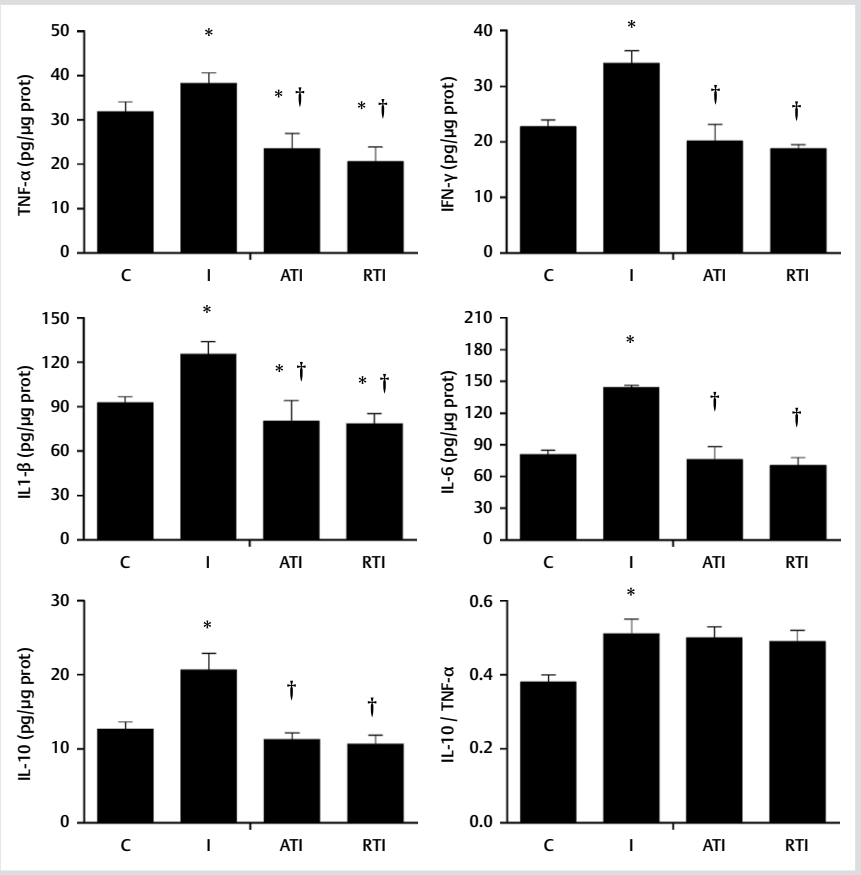

Fig. 3 Left ventricle concentration of **a** TNF-α, **b** IFN-γ, **c** IL-1β, **d** IL-6, and **e** IL-10 in control animals (C, n = 7), sedentary animals submitted to MI (I, n = 7), aerobic trained animals submitted to MI (ATI, n = 7), and resistance trained animals submitted to MI (RTI, n = 7). Two-way ANOVA and Bonferroni post-test. * $P < 0.05$ vs. C; † $P < 0.05$ vs. I.

ates the damaging effects of alcohol on the heart, improving malondialdehyde and antioxidant levels in trained rats.

Regarding cardiac remodeling, although the MI size has not been changed by resistance ET, left ventricular mass and relative wall thickness were increased. It is well established that left ventricular hypertrophy associated with resistance ET occurs in response to pressure load (in contrast to the volume load of aerobic ET), reducing the systolic burden per myofiber, and preserving normal LV wall stress [53]. In fact, systolic and diastolic ventricular function were normal after resistance ET, which is consistent with physiological hypertrophy [17]. In the present study, although left ventricular mass and relative wall thickness were increased in RTI animals, resistance ET did not modify left ventricular diastolic diameter, showing that such hypertrophy did not affect chamber size. However, these adaptations were not able to prevent ejection fraction and E/A ratio impairment after MI. We believe that differences in training volume between the aerobic and resistance exercise, along with the type of cardiovascular overload offered by both types of training may account for the different cardiovascular responses to MI.

Recently, it has been demonstrated that resistance ET (80% of one maximum repetition) increases single left ventricular myocyte dimensions and leads to faster cell contraction and relaxation, related to augmented expression of SERCA2a [29]. Thus, we may hypothesize that if our training protocol were either more intense or performed as high-volume resistance exercise some degree of cardiovascular dysfunction prevention might have been observed. However, it is not possible to know whether such a positive adaptation, as observed in the study of Melo et al. [29] can be maintained after MI. Thus, the lack of studies investigating the cardioprotective mechanisms of resistant ET against an ischemic event prevents a fuller understanding of the issue.

To our knowledge, only one study approached this issue. Utilizing a model of squat ET with electrical stimulation, Soufi et al. [49] have observed that a 12-week resistance ET elicited improved cardiac mechanical performance, coronary flow and MI area in rats undergoing ischemia-reperfusion. However, the mechanisms underlying such cardioprotection have not yet been elucidated.

Autonomic dysfunction and cardiac inflammatory profile

Although prior resistance ET was not able to prevent ventricular dysfunction triggered by MI, mortality rate was similar between both trained groups (aerobically and resistance). In order to further investigate the mechanisms associated with exercise-induced cardioprotection, we evaluated the cardiovascular autonomic nervous system of rats undergoing aerobic and resistance ET.

Our results demonstrated that prior to MI, aerobic ET prevents intrinsic heart rate decrease and baroreflex dysfunction, which may contribute to cardiac sympathetic tonus and vascular sympathetic modulation improvement, together with positive changes in vagal tonus and modulation in trained rats. Classically, aerobic ET has demonstrated positive effects on autonomic nervous system, with reduction of sympathetic discharge, increase of vagal tone, as well as baroreflex improvement, in humans [3,22,27,35] and rats [2,21,45,46] after MI or coronary artery disease.

Regarding the effects of resistance ET on cardiovascular autonomic function, their potential benefits have not been exten-

sively examined, or have presented mixed results. While eccentric resistance ET program negatively affected heart rate variability indexes in aging individuals [51], a high repetition and low load resistance ET showed positive improvements on heart rate variability, on muscle strength and endurance in coronary artery disease patients [5]. Also, our group demonstrated that dynamic resistance ET was able to improve vagal modulation to the heart and sympathetic modulation to the vessels in MI rats [17].

In the present study, resistance ET was not able to improve either spontaneous baroreflex or baroreflex sensitivity. On the other hand, this type of ET prevented an increase in sympathetic cardiovascular modulation and tonus of trained animals. These findings suggest that dynamic resistance ET may have promoted adaptations in the cardiovascular control centers, which could account for an improved cardiac and vascular autonomic control of trained animals. Our results corroborate other studies carried out in humans [5] and animals [17], thus suggesting that low-intensity resistance ET with an increased number of repetitions may be the most effective method to better promote positive adaptations to the cardiovascular autonomic nervous system.

The prevention of increased sympathetic drive to the heart and blood vessels through exercise is extremely important, since this increase has been seen to lead to adverse cardiac remodeling, associated with cell death, cytokine production, arrhythmogenesis and a sharp decline in cardiac function, along with increased prevalence of heart failure [40]. Furthermore, sympathetic overactivity contributes to the reduction of skeletal muscle blood flow, capillary recruitment, oxidative stress and inflammation, leading to skeletal myopathy and reduced exercise capacity [37]. In fact, cytokine release after MI may regulate apoptosis of myocytes, formation of collagen and matrix metalloproteinase, integrin changes, angiogenesis, and mobilization of progenitor cells, thus leading to a pathological ventricular remodeling with loss of cardiac function [38,44]. As a result, preventing the sympathetic nervous system from increasing in the heart and blood vessels may be a key factor in potential structural, biochemical and molecular changes that culminate in skeletal myopathy and heart failure.

Our results showed that both aerobic and resistance ET were able to similarly prevent left ventricle increase of pro-inflammatory cytokines TNF-α, IFN-γ, IL-1β, and IL-6 concentrations in trained rats prior to MI. In this sense, McGinnis et al. [28] have recently observed that aerobically trained mice improved heart IL-6 pathway, suggesting the involvement of this pathway in exercise preconditioning. Additionally, the prevention of sympathetic tonus increase and decreased LF band of pulse interval variability were correlated with the reduction of ventricular concentration of TNF-α in the experimental groups. Regarding this issue, norepinefrine stimulation of β2-adrenergic receptors in immune cells activates the cAMP-protein kinase A intracellular signaling pathway, which interfaces with other signaling pathways that regulate effector functions in immune cells [24]. On the other hand, it is possible that both types of ET inhibited the inflammatory process in the brain stem, thereby promoting a sympathoinhibition and lowering the production of ventricular inflammatory factors. This may indeed be possible, since the partially silencing brain *toll-like receptor 4* by intracerebroventricular injection of TLR4-SiRNA for 2 weeks conferred partial protection against ventricular remodeling with sympathoinhibition in rats with MI-induced heart failure [39].

Interestingly, the concentrations of IL-10, an important anti-inflammatory cytokine, were increased in I group, and reduced in both trained groups (ATI and RTI), culminating in IL-10/TNF-α ratio increase only in the I group. It is possible that the resolution of the post infarction inflammatory reaction has been active in animals that did not perform any type of ET, since they had increased concentrations of pro-inflammatory cytokines. However, increased IL-10 levels in I group should be interpreted with caution. Elevation of plasma IL-10 levels may suggest extensive damage by considerably increasing the production of inflammatory factors and, as such, determining a worse prognosis; however, this elevation may also be seen as a positive response to the resolution of inflammation, and, as such, contribute to a better prognosis [10,11].

We acknowledge some limitations of our study. We have not evaluated the molecular mechanisms associated with the role of the 2 types of ET in pathological cardiac remodeling, and we did not detail the inflammatory pathway triggered by MI and sympathetic hyperactivity. However, our study carried out a range of autonomic nervous system evaluations and provided a map of the main cytokines involved in the inflammatory cascade in rats trained prior to MI, particularly resistance ET. The correlations between parameters evaluating the sympathetic nervous system and the TNF-α should not be seen as having a cause-effect relationship, or as indicators of precursors of this interaction. Only studies evaluating the time course of autonomic changes and inflammatory status of rats undergoing MI may determine more precisely the mechanisms underlying neuroimmune interactions.

Conclusions

Although dynamic resistance ET did not modify cardiac function, as aerobic ET was able to, it promoted a significant decrease in the inflammatory profile of rats trained prior to MI. This remarkable effect promoted by resistance ET may be important in the prevention of chronic cardiac remodeling after MI. In addition, our study showed that both trained groups displayed decreased activity of the sympathetic nervous system to the heart and vessels, emphasizing the positive effects of aerobic and, for the first time, resistance ET in the prevention of autonomic changes triggered by MI.

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Conflict of interest: The authors declare that they do not have any conflict of interest.

Affiliations
[1] Human Movement Laboratory, Universidade São Judas Tadeu, São Paulo - SP, Brazil
[2] Hospital Materno Infantil, Universidade Federal do Maranhão, São Luís - MA, Brazil
[3] Heart Institute, Medical School of University of São Paulo, São Paulo - SP, Brazil

[4] Departamento de Fisiologia, Universidade Federal de São Paulo, São Paulo - SP, Brazil
[5] Exercise and Immunometabolism Research Group, Department of Physical Education, Universidade Estadual Paulista, Presidente Prudente - SP, Brazil
[6] Faculty of Physical Education, University of Campinas (UNICAMP), Campinas - SP, Brazil

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