

Cardiac Implications after Myocardial Infarction in Rats previously Undergoing Physical Exercise

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Abstract

Background: Few studies have analyzed the cardiac effects of exercise prior to coronary occlusion.

Objective: To evaluate the effects of myocardial infarction in rats undergoing physical exercise.

Methods: Female rats underwent swimming exercise or were kept sedentary for eight weeks and were randomized to coronary occlusion or sham surgery, in one of the following four groups: Sedentary (S), exercise (E), Sedentary myocardial infarction (SMI) and Exercise myocardial infarction (EMI). After six weeks, their biometrics, Doppler echocardiography, hemodynamics and myocardial mechanics were analyzed.

Results: No cardioprotection was observed in EMI animals and there was no difference in infarct size (%LV) between EMI ($38.50 \pm 4.60\%$) and SMI ($36.58 \pm 4.11\%$). Water content of the lung (%) of SMI (80 ± 0.59) and EMI (80 ± 0.57) was higher than that of S (78 ± 0.15) and E (78 ± 0.57) groups. Left ventricular systolic pressure (mmHg) (S: 130 ± 5 , E: 118 ± 8 ; SMI: 91 ± 3 ; EMI: 98 ± 3) and the first positive time derivative (mmHg) positive pressure (S: 8216 ± 385 ; E: 8437 ± 572 ; SMI: 4674 ± 455 ; EMI: 5080 ± 412) of S and E were higher than those of SMI and EMI. The transverse fractional shortening (%) of SMI (27 ± 2) and EMI (25 ± 2) were similar and lower than that of E (65 ± 2) and S (69 ± 2). The E/A ratio was higher in SMI (5.14 ± 0.61) and EMI (4.73 ± 0.57) compared to S (2.96 ± 0.24) and E (2.83 ± 0.21). In studies of isolated papillary muscle, depression of the contractile capacity observed was similar to that of SMI and EMI, and there was no change in myocardial stiffness.

Conclusion: Previous training by swimming did not attenuate cardiac implications due to myocardial infarction. (Arq Bras Cardiol. 2013;100(1):37-43)

Keywords: Myocardial Infarction; Physical Conditioning, Animal; Swimming, Rats.

Introduction

Cardiovascular diseases remain a major cause of morbidity and mortality worldwide¹, although several therapies have contributed to higher rates of prevention and treatment. Exercise stands out as a nonpharmacological therapy for the prevention of coronary heart diseases and for rehabilitation of already affected patients^{2,3}. It is known that individuals who perform regular physical activity have a lower incidence of heart attacks when compared with sedentary people⁴.

Although the biochemical and molecular mechanisms related to cardiac protection against myocardial infarction (MI) are still not fully understood, experimental studies have confirmed that exercise training provides protection against MI damage⁵. Some benefits described with exercise training include improved survival in mice with MI⁶, improvement in physical capacity and contractility^{7,8}, coronary flow preservation⁹,

improvement in inflammatory and antioxidant parameters¹⁰⁻¹², as well as normalization of calcium transient and improved cardiac function^{13,14}.

However, few experimental studies¹⁵⁻¹⁷ evaluated the protective effects of physical exercise prior to MI using the permanent coronary occlusion method. Recently, it was demonstrated in a study carried out in our laboratory¹⁸ that exercise performed prior to MI showed no reduction in infarction size or attenuation of the myocardial remodeling process in animals studied seven days after coronary occlusion. To the best of our knowledge, there are no studies that evaluated the influence of exercise on late ventricular remodeling. Therefore, the aim of this study was to evaluate the late cardiac structural and functional effects in rats undergoing physical exercise followed by acute myocardial infarction.

Methods

Animals

Apparently healthy three-month-old female Wistar-EPM rats weighing between 190 and 210 g were obtained from the Center for the Development of Experimental Models

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(Cedeme), Universidade Federal de São Paulo - Escola Paulista de Medicina (Unifesp - EPM). After approval by the ethics committee (0341/08), the animals were kept in plastic boxes in a room with controlled light and temperature, and provided with water and Nuvital chow (Nuvilab) *ad libitum*. Each box held a maximum of five animals distributed by randomization in four experimental groups: sedentary sham surgery (S: n = 8) exercise sham surgery (E: n = 9); sedentary myocardial infarction (SMI: n = 12) and exercise myocardial infarction (EMI: n = 10).

Physical training

The physical exercise protocol consisted of swimming in a pool built using a fiber glass water box with a diameter of 130 cm and height of 80 cm. The water was heated by a thermostat associated with a gas heating system to maintain the temperature between 32° and 34°C. On the first day of training, the rats swam for 10 minutes, with time being increased by 10 minutes/day until reaching 60 minutes on the sixth day. The training was maintained for a total period of eight weeks, five days a week, 60 min/day. A maximum of eight rats were placed simultaneously in the water box to swim. The animals were dried before being placed back in their plastic boxes¹⁹.

Surgical induction of myocardial infarction

Induction of MI followed a well-established protocol²⁰⁻²⁴. Briefly, after intraperitoneal anesthesia (ketamine 50 mg/kg and xylazine 20 mg/kg), intubation and mechanical ventilation (Harvard Rodent Ventilator, Model 863, Harvard Apparatus, Holliston, MA), thoracotomy was performed in the left hemithorax of each animal. The heart was exteriorized and ligation of the left anterior descending coronary artery was performed using 6-0 polyethylene thread.

The heart was rapidly repositioned, and the chest was closed after lung hyperinflation. The animals undergoing sham surgery went through the same surgical procedures, but without coronary ligation. The rats returned to their plastic boxes and were kept under observation for six weeks, a period that covers complete healing of MI in rats²⁵. Diagnostic confirmation of MI was performed by echocardiography, six weeks after MI was induced by surgery.

Water content of the lung and biometric analysis

Water content of the lung was obtained from their wet and dry weights. After obtaining this weight, the right lung was placed in an oven and kept for 24 hours at 80 °C. After obtaining the dry weight of the lung, the water content of the lung (%H₂O) was defined by the equation:

$$\% \text{H}_2\text{O} = (\text{wet weight} - \text{dry weight} / \text{wet weight}) \times 100$$

Body weight (BW) of each animal was determined at the end of the experimental protocol. The cardiac masses were normalized by BW: weight of the atria (AT/BW), right ventricular mass (RV/BW) and left ventricular mass (LV/BW).

Doppler echocardiography

Doppler echocardiography was performed in anesthetized rats using the same anesthetic regimen previously mentioned, six weeks after surgical induction of MI. The procedures were

performed by an observer blinded to the groups to which the animals had been assigned. A Sonos 5500 equipment (Philips Medical Systems, Andover, MA, USA) with a 12 - MHz transducer was used in a depth between 2 and 3 cm according to previously described methodology²⁰. After having their thorax shaved, the animals were placed in the left lateral position. The images were recorded on VHS videotapes and the final result was obtained from the mean of three different cardiac cycles.

The size of the MI area was obtained using two-dimensional images of the left ventricular basal transverse (at the end of the mitral valve leaflet), middle (at the papillary muscle level) and apical (distal to papillary muscle) planes, by measuring the endocardial perimeter (EP) of the ventricular cavity during diastole and the length of the arch corresponding to the infarcted segment (ISe). Three measurements were obtained from each plane and the arithmetic mean of the measurements in the three planes was considered as the infarction size (IS), expressed as a percentage, by the equation: IS (%) = ISe / EP x 100. Myocardial infarction was considered when the segment showed thickness alteration and / or abnormal myocardial systolic movement (akinesia or dyskinesia).

We considered MI with impaired segment < 40% and MI ≥ 40%. The left ventricular diastolic (DA) and systolic (SA) areas were obtained by the two-dimensional mode in the basal, middle and apical parasternal transverse planes, with the final value being the mean of three measurements in each plane. Systolic function was assessed by the transverse fractional shortening area (TFSA = DA - SA / DA), in %, with DA being the diastolic and SA the systolic area, in the three transverse planes (basal, middle and apical); the final value of each animal was the mean of three measurements in the three planes. Pulsed Doppler at the ventricular side of the mitral valve provided the flow velocity curve for analysis of diastolic function parameters such as E and A waves and E / A ratio.

Hemodynamic study

After the echocardiographic assessments, still under anesthesia, the animals were placed under mechanical ventilation (Harvard Rodent Ventilator, model 863, Harvard Apparatus, Holliston, MA) with ventilatory rate of 100 movements/minute and a tidal volume of 2.5 ml, enriched with oxygen (0.6 to 0.8 L / min).

The tip of a Millar catheter (Microtip®, 2F, Millar Instruments, Inc., Houston, USA) was placed in the left ventricle (LV) through the right common carotid catheterization. The data were obtained by AcqKnowledge® 3.7.5 software (Biopac System Inc, CA, USA) that allowed computing the instantaneous values of ventricular pressure (mmHg), end-systolic (LVESP) and diastolic (LVEDP) pressures, heart rate (bpm), positive (mmHg/s) (+dP/dt) and negative (-dP/dt) first-time derivative of the ventricular pressure of each animal.

Papillary muscle mechanics

The myocardial mechanics was assessed as previously described⁷. Briefly, the papillary muscle was carefully dissected and vertically inserted in an organ bath heated to 29 °C and oxygenated. The muscle was attached to an isometric force

transducer (Grass FT-03, Astro-Med, Inc., RI, USA) connected to a micrometer for adjustments in the resting muscle length. The composition of the Krebs-Henseleit solution was as follows (in mM): 135 NaCl; 4.69 KCl; 1.5 CaCl; MgSO₄ 1.16; KH₂PO₄ 1.18; glucose 5.50 ; HEPES 20, buffered to a pH of 7.4. The preparations were stimulated (12 times / min with a square wave of 5 ms duration) with platinum electrodes with voltages adjusted to approximately 10% more than the minimum required to produce maximum mechanical response.

After 60 minutes of stabilization at low load, the muscle was set to contract isometrically and stretched to the optimum length of its active length-tension curve (L_{max}). The tests were performed in L_{max} and isometric tension was measured by force normalized to the cross-sectional area of the muscle (g/mm²). The following parameters were obtained: peak developed tension (DT), resting tension (RT), maximum rate of development (+dT/dt) and decline in tension (-dT/dt). In addition to the baseline evaluation, the following protocols were performed:

1) length/tension relations: characterized by determination of DT (Frank-Starling curve) and RT (myocardial stiffness) at baseline (100% L_{max}) and 98%, 96%, 94% and 92% of optimum length;

2) post-pause contraction (PPC) was determined using pause lasting 30 s. The relative PPC was expressed as percentage of change in the DT observed under baseline sequential stimulation.

Statistical analysis

Data were expressed as mean \pm standard error of the mean and compared by two-way ANOVA and Tukey's post hoc test. The values of the size of LV infarcts in the SMI and EMI groups were compared by Student's *t* test. The length/ developed tension relations were evaluated by linear regression and the line slopes were compared by two-way ANOVA. The length/resting tension curves were adjusted by mono-exponential relationship using the following equation: $y = \beta_0 \times e^{Kx}$, where β_0 and K are curve constants. These nonlinear relationships were compared between groups by the values of stiffness constants (K). Statistical analyzes were performed with the aid of GraphPad Prism 4.0 (GraphPad Software Inc., San Diego, CA, USA). Differences with $p < 0.05$ were considered significant.

Results

At the end of the 14 weeks of the protocol, the body weight did not differ among the four groups (Table 1).

Infarction size

The sizes of MI in the SMI (36.58 \pm 4.11%) and EMI (38.50 \pm 4.60%) groups did not differ.

Physical exercise did not reduce the number of animals with large and moderate MI. Considering our previous experience - that infarctions $< 40\%$ do not cause substantial functional alterations when the analyses are performed six weeks after coronary occlusion - in the following functional assessments, only the animals with MI $> 40\%$ of the LV were considered. This step reduced the sample size of the SMI (n = 10) and EMI (n = 8) groups.

Water content of the lung and biometric analysis

The infarcted animals (SMI: 80 \pm 0.59%; EMI: 80 \pm 0.57%) had higher water content in the lung ($p < 0.05$) than the animals with sham surgery (S: 78 \pm 0.15 %, E: 78 \pm 0.27%), showing pulmonary edema as a result of infarction, which was not prevented by exercise.

The cardiac mass values are shown in Table 1. MI resulted in a significant increase in atrial and ventricular mass ($p < 0.001$) compared to rats undergoing sham surgery. Physical exercise resulted in left ventricular hypertrophy only in relation to S animals ($p < 0.05$). Additionally, exercise associated with MI did not prevent cardiac mass hypertrophy.

Hemodynamic study

Data on heart rate (HR) in animals from the SMI (319 \pm 12 bpm) and EMI (340 \pm 6 bpm) groups did not differ from S (349 \pm 11 bpm) animals. However, the HR of animals in group E (388 \pm 16 bpm) was significantly higher ($p < 0.05$) than that of animals in the SMI and EMI groups.

LVSP values (Figure 1A) were 31% (SMI) and 26% (EMI) lower than those in the S group, respectively, and 25% and 19% lower than those in the E group, respectively.

The SMI (4,674 \pm 455 mmHg/s) and EMI (5,080 \pm 412 mmHg/s) groups showed reduced values of + dP/dt

Table 1 – Biometric Parameters

	S (n = 8)	E (n = 9)	SMI (n = 10)	EMI (n = 8)
BW (g)	278 \pm 4	270 \pm 8	270 \pm 8	270 \pm 5
LV/BW (mg/g)	2.10 \pm 0.04	2.55 \pm 0.09*	2.40 \pm 0.05†	2.56 \pm 0.07†
RV/BW (mg/g)	0.58 \pm 0.01	0.75 \pm 0.02	1.24 \pm 0.13†	1.18 \pm 0.11†
AT/BW (mg/g)	0.12 \pm 0.01	0.11 \pm 0.01	0.33 \pm 0.05†	0.31 \pm 0.04†

Values (mean \pm sem) of cardiac mass indexed to body weight of the animals in groups sham surgery sedentary (S), sham surgery exercise (E), sedentary myocardial infarction (SMI) and exercise myocardial infarction (EMI). Body weight (BW); left ventricular weight normalized by body weight (LV/BW), right ventricular weight normalized by body weight (RV/BW), weight of the two atria normalized by body weight (AT/BW). * $p < 0.05$ in relation to group S by two-way ANOVA followed by Tukey's test; † $p < 0.001$ in relation to E group by two-way ANOVA followed by Tukey's test.

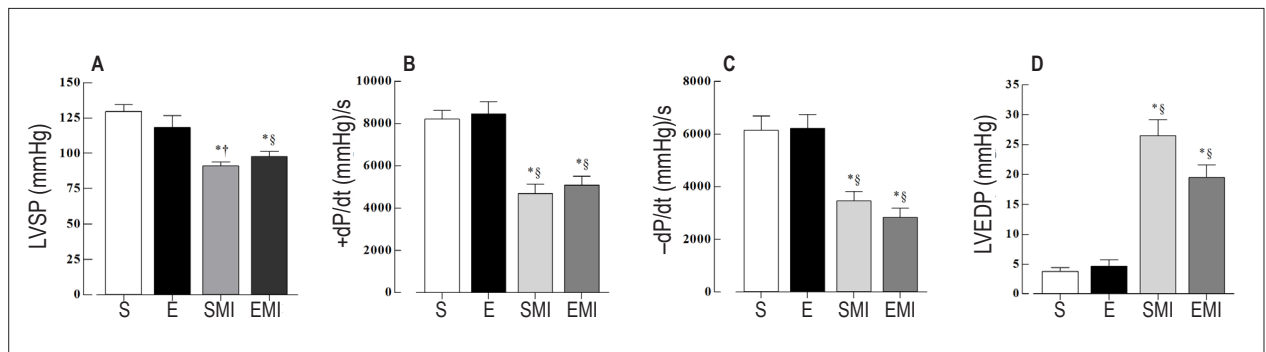


Figure 1 – Values expressed as mean \pm sem of hemodynamic parameters in the groups sedentary sham surgery (S), exercise sham surgery (E), sedentary myocardial infarction (SMI) and exercise myocardial infarction (EMI). Panel A - left ventricular systolic pressure (LVSP). Panel B - positive first-time derivative of pressure (+ dP / dt). Panel C - negative first-time derivative of pressure (- dP/dt). Panel D - left ventricular end-diastolic pressure (LVEDP). * $p < 0.001$ versus S; § $p < 0.001$ versus E; † $p < 0.01$ vs. E by two-way ANOVA followed by Tukey's test."

(Figure 1B) compared to the S ($8,216 \pm 385$ mm Hg/s) and E ($8,437 \pm 572$ mm Hg/s) groups.

Similar results were observed regarding -dP/dt (S: $6,151 \pm 543$ mmHg/s = E: $6,212 \pm 540$ mmHg/s > SMI: $3,463 \pm 358$ mmHg/s = EMI: $2,833 \pm 343$ mmHg/s) as shown in Figure 1C. Additionally, LV end-diastolic pressure (Figure 1D) was significantly higher ($p < 0.001$) in infarcted animals (SMI: 22.5 ± 3.3 mmHg and EMI: 17.6 ± 2.0 mmHg) compared to non-infarcted animals (S: 3.7 ± 0.7 mmHg and E: 4.7 ± 1.0 mmHg). Together, the hemodynamic data indicate systolic and diastolic dysfunction induced by MI and not prevented by physical exercise.

Echocardiographic analysis

The diastolic areas of the infarcted groups (SMI: 0.611 ± 0.041 cm²; EMI: 0.680 ± 0.028 cm²) were significantly higher than the areas in the sham groups (S: 0.342 ± 0.011 cm², E: 0.416 ± 0.024 cm²). The systolic areas of the S (0.107 ± 0.007 cm²), and E (0.148 ± 0.012 cm²) groups were statistically lower than the areas of the infarcted groups (SMI: 0.447 ± 0.034 cm²; EMI: 0.508 ± 0.021 cm²), as shown in Figures 2A and 2B.

The values relative to FAC (Figure 2C) of infarcted groups (SMI: $27 \pm 2\%$; EMI: $25 \pm 2\%$) were significantly lower

compared to the groups of animals with sham surgery (S: $69 \pm 2\%$, E: $65 \pm 2\%$). Additionally, the E/A ratio (Figure 2D) of infarcted animals (SMI: 5.14 ± 0.61 ; EMI: 4.73 ± 0.57) were significantly higher ($p < 0.001$) compared to groups with sham surgery (S: 2.96 ± 0.24 , E: 2.83 ± 0.21). The results, considered together, indicate LV dilatation and confirm hemodynamic impairment of systolic and diastolic function caused by MI, not attenuated by exercise.

Myocardial mechanics

There was no difference between the cross-sectional areas of the papillary muscles (S: 0.75 ± 0.09 , E: 0.76 ± 0.12 , SMI: 0.81 ± 0.11 , EMI: 0.92 ± 0.16 ; mm²). However, as shown in Table 2, the values corresponding to DT, +dT / dt, -dT/dt on L_{max} for Groups S and E were significantly higher than those of SMI and EMI groups. There was no statistical difference between the groups in relation to RT.

As shown in Figure 3A, DT was designed as a function of different muscle lengths. There was a linear correlation between muscle length and DT in all groups (the lowest r value was 0.6536). For the SMI and EMI groups, the developed length/tension correlations were lower when compared to groups S and E, indicating that for the same

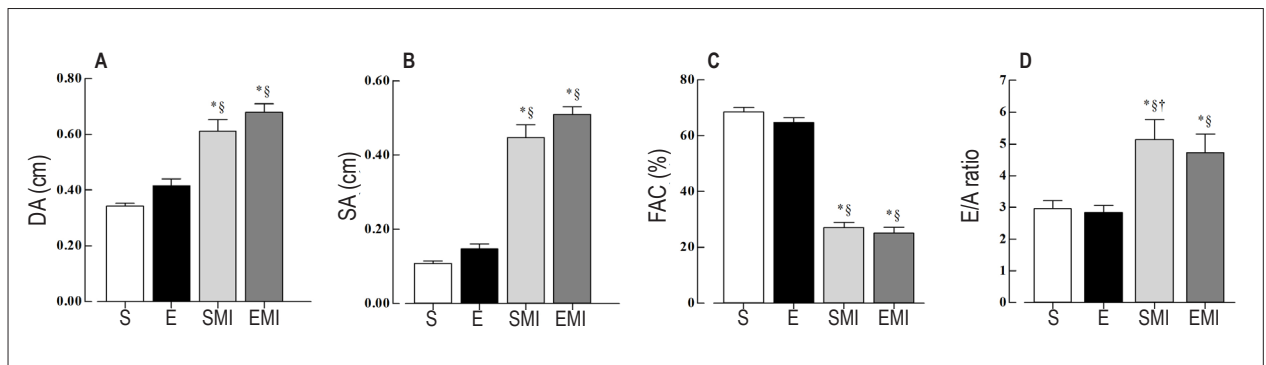


Figure 2 – Values (mean \pm sem) of echocardiographic parameters of groups sedentary sham surgery (S), exercise sham surgery (E), sedentary myocardial infarction (SMI) and exercise myocardial infarction (EMI). Panel A - left ventricular end-diastolic area (DA). Panel B - left ventricular end-systolic area (SA). Panel C - fractional area of change (FAC) Panel D - E/A ratio (E/A). * $p < 0.001$ versus S; § $p < 0.001$ versus E; † $p < 0.01$ versus E by two-way ANOVA followed by Tukey's test.

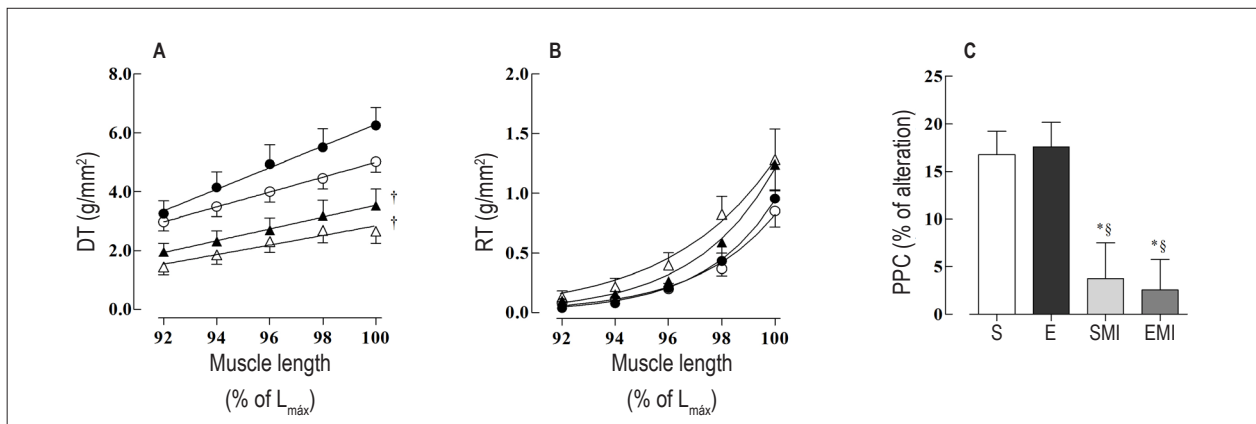


Figure 3 – Stretching/active tension curves (Panel A) and resting tension (Panel B) of the four groups: sedentary group (○), exercise group (●), the sedentary MI (Δ) and exercise MI group (▲). Panel C - Percentage variation in post-pause contraction (PPC) compared to baseline contractions, after 30 seconds of pause for sedentary (S), exercise (E), sedentary myocardial infarction (SMI) and exercise myocardial infarction (EMI) groups. Values expressed as mean ± sem. * p < 0.01 versus S; † p < 0.01 versus E; ‡ p < 0.001 versus E by two-way ANOVA followed by Tukey's test.

level of stretching, greater force is generated in groups S and E. The slope of the curves (g/mm²/L_{max}%) of group E (0.3670 ± 0.394) was higher than those in groups SMI (0.2009 ± 0.0465) and EMI (0.1666 ± 0.0301). The slope of S (0.2527 ± 0.0256) was not different from the slopes of E, SMI and EMI. Therefore, it is possible to consider that, for the same length at rest, the papillary muscles in group E are able to generate higher tension, i.e., recruitment of the Frank-Starling mechanism is more pronounced in animals undergoing exercise.

The length/tension curves at rest were similar between the groups, demonstrating that infarction and exercise did not affect myocardial stiffness (Figure 3B). PPC values (Figure 3C) were significantly reduced in the SMI (4 ± 4%) and EMI (3 ± 3%) groups, when compared to S (17 ± 2%) and E (18% ± 3%) groups, indicating loss of Ca²⁺ kinetics in the infarcted groups.

Discussion

The results of the present study indicate that physical exercise by swimming, prior to MI, did not attenuate the MI-induced alterations in rats, such as MI size, pulmonary congestion, cardiac remodeling and systolic and diastolic dysfunction. These results differ from those observed in other studies¹⁵⁻¹⁷. McElroy et al¹⁵, Dayan et al¹⁶ and Freimann

et al¹⁷ described that in exercised male rats the MI size was attenuated compared to sedentary rats. McElroy et al¹⁵ also described that this finding was accompanied by increased capillary density.

Studies^{26,27} have shown that is possible that gender difference was significant for the differences found in this study. Paroo et al²⁷ reported that exercise after MI improved ventricular performance and reduced LV end-diastolic pressure in male rats, but not in females. Thorp et al²⁸ described that male rats undergoing treadmill training showed increased myocardial tolerance to ischemia/reperfusion, whereas female rats showed no benefit.

Another possibility would be related to the duration of the exercise protocol²⁹. There is evidence that the longer the training, the greater the benefits. For instance, mice undergoing two weeks of voluntary exercise³⁰ exhibited no changes in the MI area and remodeling. The animals in Dayan et al study¹⁶ swam for three weeks and did not exhibit attenuation of MI size or hypertrophy, but showed improvement in LV geometry and systolic function. The animals in McElroy et al¹⁵ and Freimann et al¹⁷ studies that swam for five and seven weeks, respectively, showed significant reductions in the size of MI. As the duration of our exercise protocol was similar to those used by these two authors and we did not observe cardioprotection

Table 2 - Mechanics of the papillary muscle in L_{max}

	S (n = 8)	E (n = 9)	SMI (n = 10)	EMI (n = 8)
DT (g/mm ²)	5.27 ± 0.28	6.24 ± 0.61	3.17 ± 0.48 [†]	2.65 ± 0.40 [†]
RT (g/mm ²)	0.90 ± 0.12	0.95 ± 0.06	1.28 ± 0.25	1.24 ± 1.21
+dT/dt (g/mm ² /s)	49 ± 4	58 ± 7	25 ± 4 [†]	27 ± 4 [†]
-dT/dt (g/mm ² /s)	20 ± 2	29 ± 5	15 ± 2 [†]	17 ± 3 [†]

Values (mean ± sem) of developed tension (DT); resting tension (RT); maximal rate (+dT/dt) of developed tension and decline (-dT/dt) in the groups sedentary (S), exercise (E), sedentary myocardial infarction (SMI) and exercise myocardial infarction (EMI). * p < 0.01 in relation to group S by two-way ANOVA followed by Tukey's test; † p < 0.001 in relation to group E by two-way ANOVA followed by Tukey's test.

by exercise, we cannot consider that this factor has interfered with our results.

Recently, in our laboratory, Bocalini et al⁷ demonstrated that healthy rats undergoing eight weeks of swimming showed complete loss of the benefit of physical capacity, remodeling and myocardial mechanical function when analyzed after two weeks of detraining. The complete loss of the alterations induced by exercise training was also observed at the cellular level³¹. These data can raise the hypothesis that throughout the six weeks of recovery after MI, the infarcted rats in the present study may have lost the beneficial alterations promoted by swimming described by other authors^{7,15-17,32}. However, this conclusion does not hold if we consider that in experiments with four-week periods of detraining¹⁶, a beneficial effect of prior exercise was observed. Moreover, ischemic conditioning, with which cardioprotection is more transitory than that obtained with exercise, has beneficial effects that have been well identified in analyses carried out weeks after the ischemic insult³³.

To our knowledge, this seems to be the first study to show that exercise performed prior to MI does not attenuate the damage to myocardial mechanics in the papillary muscles of infarcted rats. Our data show that the response of the papillary muscle of infarcted sedentary or exercised rats is depressed. The PPC (Figure 3C) allows indirect evaluation of the kinetics of calcium. In the normal rat myocardium, the potentiation of PPC is due to the further increase in Ca^{2+} in the sarcoplasmic reticulum (SR) during the longer break, as a result of the activity of the SR Ca^{2+} -ATPase (SERCA2) and increased³⁴ fractional release of Ca^{2+} . Moreover, PPC is

negatively modulated by Ca^{2+} efflux via Na^+ / Ca^{2+} (NCX). Reductions in SERCA2 or increases in NCX may reduce PPC. Recently, a study carried out in our laboratory²⁴ showed that, after myocardial infarction, there was a decrease in SERCA2 accompanied by an increase in NCX, allowing us to understand the PPC reduction observed in this study.

Furthermore, our results show changes in the slopes of the stretch/tension ratios developed between the infarcted and E groups, suggesting an influence on the sensitivity of Ca^{2+} myofilaments. Studies have showed impairment of the Frank-Starling mechanism in humans^{35, 36} and dogs³⁷ with infarcted hearts.

We conclude that physical exercise performed by female rats, prior to MI, did not reduce infarct size or attenuate the late myocardial damage secondary to myocardial infarction.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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