CLINICS

BASIC RESEARCH

Aerobic exercise improves the inflammatory profile correlated with cardiac remodeling and function in chronic heart failure rats

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OBJECTIVE: The aim of the present study was to evaluate the effect of 8 weeks of aerobic exercise training on cardiac functioning and remodeling and on the plasma levels of inflammatory cytokines in chronic heart failure rats.

METHODS: Wistar rats were subjected to myocardial infarction or sham surgery and assigned to 4 groups: chronic heart failure trained (n = 7), chronic heart failure sedentary (n = 6), sham trained (n = 8) and sham sedentary (n = 8). Four weeks after the surgical procedures, the rats were subjected to aerobic training in the form of treadmill running (50 min/day, 5 times per week, 16 m/min). At the end of 8 weeks, the rats were placed under anesthesia, the hemodynamic variables were recorded and blood samples were collected. Cardiac hypertrophy was evaluated using the left ventricular weight/body weight ratio, and the collagen volume fraction was assessed using histology.

RESULTS: The chronic heart failure trained group showed a reduction in left ventricular end-diastolic pressure, a lower left ventricular weight/body weight ratio and a lower collagen volume fraction compared with the chronic heart failure sedentary group. In addition, exercise training reduced the plasma levels of TNF-α and IL-6 and increased the plasma level of IL-10.

CONCLUSION: An 8-week aerobic exercise training program improved the inflammatory profile and cardiac function and attenuated cardiac remodeling in chronic heart failure rats.

KEYWORDS: Exercise; Inflammation; Heart Failure.

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INTRODUCTION

Chronic heart failure (CHF) is a clinical syndrome characterized by left ventricular (LV) dysfunction and a marked reduction in physical capacity. Systemic disorders occur in CHF, such as hemodynamic alterations, intrinsic skeletal muscle abnormalities and high levels of circulating proinflammatory cytokines, which are related to exercise intolerance (1-3). Several studies have shown a direct association between proinflammatory cytokines, especially tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), and the progression of CHF syndrome. The immune activation is related to low peripheral perfusion leading to an increase in proinflammatory cytokines and catecholamines, contributing to the abnormalities in hemodynamic variables and cardiac structure that result in the worsening of CHF (4-5). In addition, CHF-related cardiac remodeling can result in cardiac hypertrophy, changes in the extracellular matrix with collagen accumulation, ventricular dilatation and impaired systolic and/or diastolic functioning (6).

Regular physical training is closely associated with the attenuation of LV dilatation, the reduction of cardiac hypertrophy and myocardial fibrosis and the slow progression of coronary artery disease (7-8). Furthermore, physical training can have beneficial effects on neurohumoral, inflammatory, metabolic and central hemodynamic responses and on endothelial, skeletal muscle and cardiovascular functions in CHF patients (9). Regular physical training is closely associated with increases in myocardial perfusion and metabolism and the normalization of the sympathetic-parasympathetic balance, which decrease oxidative stress. Moreover, it can be related to improved myocardial calcium handling (10-11). Furthermore, several studies have reported that aerobic exercise has an anti-inflammatory effect, mainly by decreasing inflammatory

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cytokine levels and increasing anti-inflammatory cytokine levels in CHF (12-14).

Improvements in the interleukin-10 (IL-10)/TNF-α ratio were recently observed in the skeletal muscle of CHF rats after 8 weeks of treadmill exercise training; these improvements led to both a reduction in TNF-α and an increase in IL-10 (15). The local inflammatory process appears to begin in the peripheral skeletal muscle as a response to low perfusion, and increased reactive oxygen species could contribute to an increased systemic (plasmatic) proinflammatory profile (16).

Physical exercise improves skeletal muscle perfusion (17) and reduces oxidative stress and inflammation (18), resulting in better physical performance; consequently, an exercise program could be beneficial for conditions associated with proinflammatory activation, such as that observed in CHF. However, to the best of our knowledge, no studies in the literature demonstrate the effects of physical training on the plasmatic inflammatory profile and cardiac remodeling or the correlation between these variables in rats with CHF; therefore, the benefits of physical training have not been fully clarified. In addition, exercise training's effect on improvements in LV dysfunction, myocardial fibrosis and hemodynamic changes in CHF needs to be clarified. Therefore, the aim of the present study was to evaluate the effects of 8 weeks of aerobic exercise training on the hemodynamic functioning, cardiac remodeling and plasmatic levels of IL-6, TNF-α and IL-10 in an animal model of chronic heart failure subsequent to myocardial infarction.

METHODS

Animals

A total of 29 male Wistar rats weighing between 230 to 280 g obtained from the Animal Breeding Unit at the Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA) were used in this study. The rats were housed under standard conditions, as described previously (14).

Experimental design

Myocardial infarction (MI) was induced via left anterior descending coronary artery ligation. The sham groups underwent the same surgical procedure without artery ligation, as described previously (14). The animals were divided into 4 experimental groups: CHF trained rats (CHF-Tr, n = 7), CHF sedentary rats (CHF-Sed, n = 6), sham trained rats (Sham-Tr, n = 8) and sham sedentary rats (Sham-Sed, n = 8).

Aerobic exercise training protocol

Four weeks after the myocardial infarction surgery, the groups of trained animals underwent aerobic exercise training sessions by running on a treadmill over an 8-week period. The exercise sessions were conducted 5 times per week and lasted 50 min per session at 16 m/min (8), representing an aerobic protocol and corresponding to an intensity of 55% VO_2max, as described previously (19). On the first week of training, all of the rats ran for 20 min. During the subsequent weeks of training, the running time was extended by 10 min per week until all of the rats were running for 50 min/day.

Hemodynamics, infarct size, edema evaluation and cardiac hypertrophy

Hemodynamic measurements: The animals were anesthetized with ketamine (90 mg/kg, i.p.) and xylazine (12 mg/kg, i.p.). A catheter connected to a pressure transducer was placed in the right carotid artery. After 5 min, the catheter was placed in the LV cavity to measure the arterial and ventricular pressures. Blood samples were collected via a catheter positioned in the right carotid artery and then stored at -20℃. The myocardial infarction area was evaluated using planimetry (20), and pulmonary and hepatic congestion were evaluated using the wet/dry weight ratio. All of the procedures were conducted in accordance with those used in a previous study (14). Cardiac hypertrophy was evaluated using the LV weight (LVW): body weight (BW) ratio.

Determination of total myocardial collagen content

Cryostat sections (6 μm) of myocardial tissue were stained with picrosirius red (PSR). The collagen measurements were obtained from digitized images (40× magnification lens) collected using a camera attached to an Olympus BX 50 microscope. Forty microscopic fields were analyzed in the myocardial noninfarcted area, and perivascular collagen was excluded. The total collagen volume fraction was obtained using computerized image analysis software (Image Pro plus 4.5, Media Cybernetic Inc., Silver Spring, MD) and quantified as the percentage per field.

Determination of plasma cytokine levels

The plasma levels of TNF-α, IL-6 and IL-10 were determined with a multiplex bead array using Milliplex™ MAP rat cytokine kits (RCYTO-80K; Millipore, Billerica, MA, USA). Milliplex™ MAP is based on Luminex® xMAP™ technology, as recommended by the manufacturers. All cytokines are reported as pg/ml.

Statistical analysis

The data are presented as the mean ± SD. The data were tested for normal distribution using the Kolmogorov-Smirnov test. One-way ANOVA and the Student-Newman-Keuls post-hoc test were used to compare the groups. A p-value less than 0.05 was considered statistically significant. Relationships between variables were assessed using Pearson correlation coefficients. The GraphPad Prism 5 program (GraphPad Software, San Diego, California, USA) for Windows was used as a computational tool for the data analysis.

Ethical information

All of the procedures outlined in this study were approved by the Ethics Committee Research of the UFCSPA (protocol 620/08).

RESULTS

Mortality, body weight, infarct size, cardiac hypertrophy and pulmonary and hepatic congestion

The mortality rate within 24 h after the infarct surgery was 21%. No significant differences in body weight were found among the 4 groups at the end of the study. The mean infarct size in both CHF groups was greater than 35% of the

LV, and no significant difference was found between the trained and sedentary CHF groups ($p>0.05$). At the end of the study, the LVW/BW ratio was higher in the CHF-Sed group compared with the other three groups ($p<0.05$). Similarly, the CHF-Sed group showed a higher percentage of water in the lungs and liver (pulmonary and hepatic congestion; $p<0.05$) c'ompared with the other groups. These data are summarized in Table 1.

Hemodynamic variables

Table 2 presents all of the hemodynamic data. The CHF groups (trained and sedentary) showed higher values of left ventricular end diastolic pressure (LVEDP) compared with the sham groups ($p<0.05$). However, when the CHF-Tr group was compared with the CHF-Sed group, a lower LVEDP ($p<0.05$) was observed in the trained group. The positive derivative of LV pressure ($+dP/dt_{max}$) was higher in the sham groups compared with the CHF-Sed group. However, the CHF-Tr group did not show a difference compared with the Sham-Sed group. The negative derivative of LV pressure ($-dP/dt_{max}$) was lower in the CHF-Sed group compared with the sham groups. No differences were found in the LV systolic pressure (LVSP), systolic blood pressure (SBP) or diastolic blood pressure (DBP). All hemodynamic variables were assessed while the rats were under anesthesia.

Plasma cytokine levels

The plasma levels of IL-10 were higher in the Sham-Tr and CHF-Tr groups compared with their sedentary counterparts (Sham-Sed and CHF-Sed, Figure 1A). The plasma levels of TNF-α were higher in the CHF-Sed group

Table 1 - Body weight, myocardial infarct size, pulmonary and hepatic congestion and cardiac hypertrophy of the 4 studied groups of Wistar rats.

Parameters	Sham-sed	Sham-Tr	CHF-sed	CHF-Tr	F(3,26)	*p*-value
Body weight (g)	344±43	340±23	333±34	333±10	0.22	0.88
MIS (%)	0	0	37±3	36±3	900.9	0.0001
PC (%)	73.6±1	73.63±2	77.2±1*	74±2	7.55	0.0009
HC (%)	70.2±1	70.7±1	72±1*	70±1	10.43	0.0001
LVW:BW (mg/g)	2.39±0.3	2.36±0.2	3.14±0.5*	2.69±0.2	8.81	0.0004

Values are the means ± SD. MIS, myocardial infarct size; PC, pulmonary congestion; HC, hepatic congestion; LVW:BW, left ventricular weight: body weight. *$p<0.05$ compared with all groups. One-way ANOVA followed by Student-Newman-Keuls post-hoc test was used for the statistical analysis.

Table 2 - Hemodynamic variables.

Hemodynamic	Sham-sed	Sham-Tr	CHF-sed	CHF-Tr	F(3,26)	*p*-value
LVEDP (mmHg)	4.6±2.7	5.7±4.6	30.1±7.7*†	21.1±8.7*	27.59	0.0001
LVSP (mmHg)	112.9±14	117.5±19	102.7±11	113.1±12	1.55	0.23
$+dP/dt_{max}$ (mmHg/s)	5875±1133	6570±1824	3822±704*	4750±1387§	5.88	0.003
$-dP/dt_{max}$ (mmHg/s)	-3772±600	-3982±878	-2562±534*	-2941±884*	5.10	0.007
SBP (mmHg)	119±20	105±15	102±15	110±14	1.10	0.37
DBP (mmHg)	93±17	81±11	82±10	91±11	1..43	0.26

Values are the mean ± SD. LVEDP, left ventricular end-diastolic pressure; LVSP, left ventricular systolic pressure; $+dP/dt_{max}$, maximum positive left ventricular derivate; $-dP/dt_{max}$, maximum negative left ventricular derivate; SBP, systolic blood pressure; DBP, diastolic blood pressure. *$p<0.05$ *vs.* sham groups; †$p<0.05$ *vs.* CHF-Tr group; § $p<0.05$ *vs.* sham-tr group. One-way ANOVA followed by Student-Newman-Keuls post-hoc test was used for the statistical analysis.

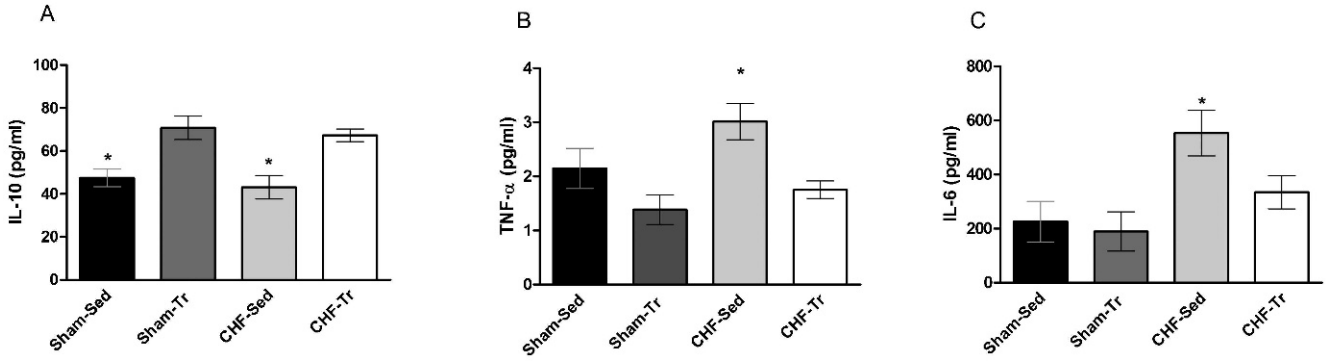

Figure 1 - Mean data showing the effects of exercise training on the plasmatic levels of anti- and pro-inflammatory cytokines. A) Interleukin-10 (IL-10); $F(3,21)=9.039$, $p=0.0006$; *$p<0.05$ *vs.* CHF-Tr and Sham-Tr; B), Tumor Necrosis Factor-alpha (TNF-α); $F(3,21)=5.587$, $p=0.006$; *$p<0.05$ *vs.* all groups; C) interleukin-6 (IL-6); $F(3,21)=4.932$, $p=0.001$; *$p<0.05$ *vs.* all groups. Values are the means ± SD. One-way ANOVA followed by Student-Newman-Keuls post-hoc test was used for the statistical analysis.

compared with all other groups (Figure 1B). Additionally, the plasma levels of IL-6 were higher in the CHF-Sed group compared with all other groups (Figure 1C).

The IL-10/TNF-α ratio was lower in the CHF-Sed group compared with the Sham-Tr and CHF-Tr groups (Figure 2). The Sham-Sed group also showed lower IL-10/TNF-α ratio values compared with the Sham-Tr group. The increase in the IL-10/TNF-α ratio in the trained groups was related to both an increase in the plasma levels of IL-10 and a decrease in the plasma levels of TNF-α (Figure 1A and B), suggesting that exercise training has an important systemic anti-inflammatory effect.

Correlations

A significant positive correlation was found between LVEDP and LVW/BW ($r = 0.84$, $p<0.01$, Figure 3A), TNF-α and LVW/BW ($r = 0.83$, $p<0.0001$, Figure 3B) and IL-6 and LVW/BW ($r = 0.89$, $p<0.0001$, Figure 3C).

Myocardial collagen content

The percentage of the total collagen volume fraction was significantly lower in the CHF-Tr group than in the CHF-Sed group ($p<0.05$; 0.72 ± 0.1 *vs.* $1.16 \pm 0.2\%$, respectively; Figure 4 E).

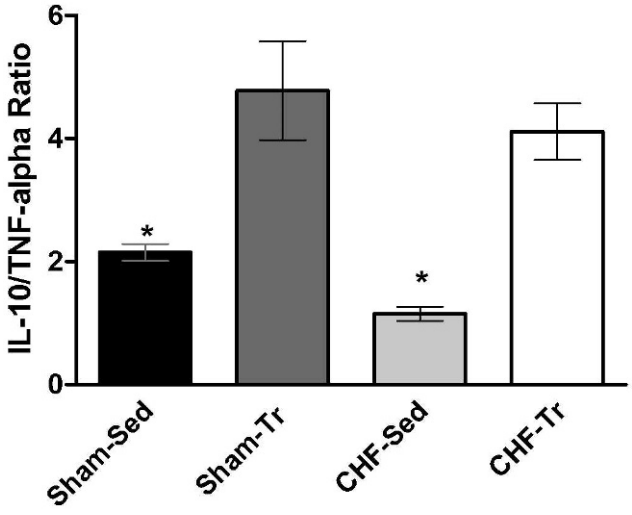

Figure 2 - IL-10:TNF-α ratio. $F(3,21) = 12.78$, $p = 0.0001$. Values are the mean ± SD.* $p<0.05$ *vs.* Sham-Tr and CHF-Tr.

DISCUSSION

The main finding of the present report was that exercise training was able to prevent ventricular remodeling and promote an anti-inflammatory effect in the CHF rats, as shown by the following findings: 1) a reduction in LVEDP and the LVW/BW ratio, 2) a lower collagen volume fraction, 3) a positive association between LVEDP and LVW/BW, 4) an increase in IL-10 and decreases in the TNF-α and IL-6 plasma levels and 5) improvements in the IL-10/TNF-α ratio in both the sham and CHF trained groups.

Chronic heart failure subsequent to myocardial infarction is the most common experimental model used for studying heart failure syndrome. This model produces a marked LV dysfunction that is directly related to the myocardial infarct size (21-22). In our study, we used the classical technique of coronary artery ligation, which resulted in a total infarct area of approximately 35% of the left ventricle in both the sedentary and trained CHF groups. A significant increase in the end-diastolic pressure values of the left ventricle (greater than 20 mmHg) was observed. This increase demonstrated a severe impairment in cardiac functioning, which characterizes the development of CHF (23). In addition, in the present study, we observed impairments in $-dP/dt_{max}$ and $+dP/dt_{max}$ in CHF.

Exercise training reduced the LVEDP (29.9%) and the LVW/BW ratio (14%) in the CHF rats. Additionally, in the present report, we found a positive association between LVEDP and the LVW/BW ratio. In the sedentary CHF rats, we found evidence that higher LVEDP values promote LV hypertrophy. Interestingly, after training, a reduction in both LVEDP and the LVW/BW ratio was observed, which can be associated with improvements in cardiac remodeling. Moreover, in the present study, exercise training showed a positive effect on $+dP/dt_{max}$ in the CHF rats. Pathological cardiac hypertrophy in CHF involves cellular and molecular remodeling, which are accompanied by changes in the extracellular matrix and by myocyte death caused by necrosis and apoptosis. As the heart undergoes the transition from compensated hypertrophy to dilated heart failure, these cellular changes intensify, resulting in myocyte lengthening, LV dilatation and impaired systolic and diastolic functioning (6). The accumulation of collagen in the extracellular space contributes to alterations in the electrical and mechanical properties of the heart, which lead to contractile function impairment and cardiac stiffness in CHF (8). In our study, aerobic exercise training attenuated the total collagen volume fraction and LV hypertrophy, both of which are associated with cardiac remodeling in CHF

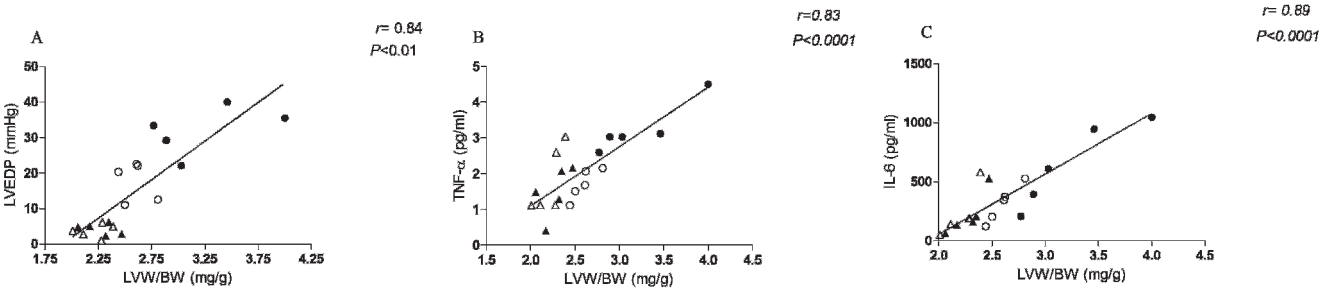

Figure 3 - Correlations among A) left ventricular weight (LVW):body weight (BW) and left ventricular end-diastolic pressure (LVEDP), B) TNF-α and LVW:BW, and C) IL-6 and LVW:BW of sham sedentary rats (▲), sham trained rats (△), chronic heart failure trained rats (○) and chronic heart failure sedentary rats (●).

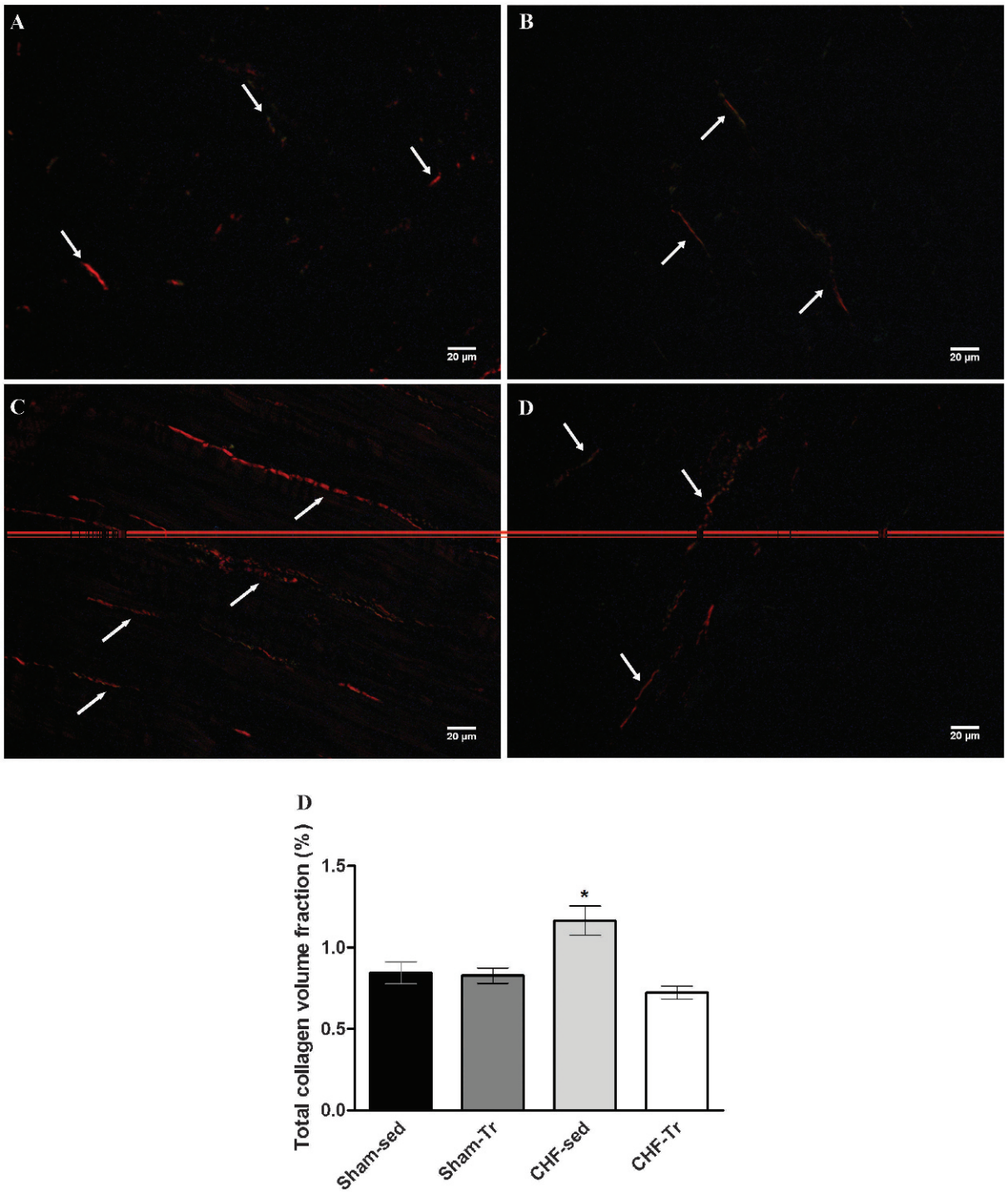

Figure 4 - Representative picrosirius red-stained ventricular sections under polarized light. A) Sham-Sed group; B) Sham-Tr group; C) CHF-Sed group, D) CHF-Tr group and E) statistical analysis. $F(3,17) = 8.811$, $p = 0.001$. Values are the mean $\pm$ SD.* $p<0.05$ *vs.* all groups. One-way ANOVA followed by Student-Newman-Keuls post-hoc test was used for the statistical analysis.

rats. In this study, we found a significant and positive correlation between the LVW/BW ratio and LVEDP, which confirms the relationship between morphological and functional changes in the rat model of CHF. These effects are most likely associated with myocardial fibrosis reduction and cardiomyocyte length and width, indicating a reversal of the pathologic hypertrophy present in CHF, as previously shown (24). Thus, aerobic exercise training exerts a positive effect on cardiac remodeling and prevents impairments in cardiac functioning. A recent meta-analysis (25) showed that aerobic training had a positive effect on the ejection fraction and end-diastolic and end-systolic volumes in individuals with clinically stable CHF. These improvements were associated with an increase in the functional capacity, which was attributed to a reduction of cardiac remodeling.

Functional limitations in CHF could be related, at least in part, to muscular and vascular dysfunction (26-27) and to a pro-/anti-inflammatory imbalance (28). Regarding the inflammatory profile observed in CHF in our study, we found higher plasma levels of TNF-α and IL-6 and a lower plasma level of IL-10 in only the CHF-sed group 14 weeks after the myocardial infarction. The chronic systemic proinflammatory state could result in skeletal muscle atrophy and cardiac cachexia, which increase morbidity and mortality (29). An increase in the concentration of inflammatory cytokines is related to LV dysfunction, LV dilatation, the activation of fetal gene expression, cardiac myocyte hypertrophy and myocyte apoptosis, all of which contribute to the progression of CHF (30). Muscle contraction during regular physical exercise results in muscle-derived IL-6 production, which leads to an increase in other anti-inflammatory cytokines in the plasma, such as IL-10 and IL-1ra and results in the inhibition of TNF-α production (31). In the present study, the reduced level of LV hypertrophy could be explained by improvements in the pathologic scenario that include the lower plasma levels of TNF-α and IL-6 and increased plasma levels of IL-10 observed after the exercise training period in the CHF rats. These results were confirmed by the observed relationship between the inflammatory cytokines (IL-6, TNF-α) and LV hypertrophy.

The present study has limitations that warrant discussion. First, echocardiography was not used to evaluate the changes in ventricular diameter. Second, cardiac hypertrophy was not assessed using a histological technique. Such an assessment could provide more accurate data for identifying cardiac hypertrophy. However, we did observe changes in cardiac mass via the LVW/BW ratio, which can predict cardiac remodeling and the effects of exercise training on the myocardial tissue in CHF.

In conclusion, CHF-induced rats that underwent 8 weeks of aerobic physical training showed improved cardiac functioning and attenuated cardiac remodeling, as shown by reductions in LVEDP, LV hypertrophy and LV collagen volume fraction. These changes may have contributed to a reduction in pulmonary and hepatic congestion. Similarly, the exercise training regimen ameliorated the inflammatory profile. These results indicate that physical exercise played a pivotal role in the control of the chronic systemic inflammation observed in heart failure syndrome. Consequently, our findings provide an important contribution to the understanding of the positive effects of regular aerobic exercise training for CHF.

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AUTHOR CONTRIBUTIONS

Nunes RB was responsible for the study design, statistical analysis, molecular biological analysis, data evaluation and collection, manuscript writing and critical review. Alves JP contributed to the study design, statistical analysis, molecular biological analysis, data evaluation and collection and manuscript critical review. Kessler LP contributed to the molecular biological analysis, data evaluation and manuscript writing and critical review. Dal Lago P contributed to the study design, statistical analysis and manuscript writing and critical review.

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