

## ORIGINAL ARTICLE

## Physical Training Improves Cardiac Structure and Function of Rats After Doxorubicin-Induced Cardiomyopathy

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### Abstract

**Background:** The use of doxorubicin in chemotherapy has been associated with cardiotoxicity and heart failure. Physical exercise produces favorable morphofunctional adaptations in the cardiovascular system and may reverse cardiac dysfunction in patients undergoing chemotherapy.

**Objective:** To assess the effects of physical training on myocardial structure, cardiac function, and exercise tolerance in Wistar rats initiated after the onset of cardiotoxicity-induced cardiotoxicity.

**Methods:** This study investigated 30 adult male Wistar rats randomly divided into four groups: control (C), exercise (EX), doxorubicin (DX), and doxorubicin and exercise (DXEX). The DX and DXEX groups received six doses of doxorubicin from 1.25 mg/kg body weight up to a cumulative dose of 7.5 mg/kg. Injections were administered intraperitoneally three times a week for two weeks; after this stage, the EX and DXEX groups started physical training (swimming) sessions three times a week with a load of 5% of their body weight. Echocardiography and exercise tolerance tests were performed. Generalized linear models were used in statistical analysis, and a  $p < 0.05$  was set as statistically significant.

**Results:** Left ventricular shortening fraction and ejection fraction were reduced in the DX group compared to C, EX, and DXEX. The DXEX group showed greater tolerance to effort when compared to the DX and C groups.

**Conclusion:** Physical training, initiated after the onset of doxorubicin-induced cardiotoxicity, improved cardiac function and exercise tolerance in rats.

**Keywords:** Anthracyclines; Cardiotoxicity; Echocardiography; Exercise.

### Introduction

Doxorubicin is an antibiotic of the anthracycline class used to treat neoplasms. However, the clinical use of this drug may be limited by the development of dose-dependent cardiotoxicity.<sup>1</sup> Among the interventions to minimize doxorubicin-induced cardiotoxicity, physical exercise initiated before chemotherapy has been recommended as part of a comprehensive multidisciplinary therapeutic program. This non-pharmacological strategy can improve tolerance to

chemotherapy, protect the heart, and mitigate potential toxic effects.<sup>2</sup>

The mechanisms by which exercise protects the heart are not yet fully understood. However, it is known that exercise can positively and interactively modulate cardiac defense and adaptation, which seem to antagonize the toxic effects of doxorubicin.<sup>3</sup> Physical exercise performed before doxorubicin administration improves mitochondrial function, decreases the production of reactive oxygen species, oxidative damage and apoptosis, preserves alpha-myosin heavy chain, decreases left ventricular end-

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systolic pressure, and improves the time derivative of ventricular pressure (dP/dt).<sup>4-6</sup>

However, despite the recommendation of physical exercise to treat heart failure by the Brazilian Cardio-Oncology Guidelines of the Brazilian Society of Cardiology<sup>7</sup> and the American College of Cardiology/American Heart Association guidelines for the diagnosis and management of heart failure in adults,<sup>8</sup> few studies<sup>6,9</sup> have evaluated the effects of physical training performed after doxorubicin administration on cardiotoxicity.

Among these studies, Lee et al.<sup>9</sup> suggest that the exercise-mediated effects against doxorubicin-induced cardiotoxicity is associated with improved basal autophagy/mitophagy and antioxidative capacity via NADPH oxidase 2 downregulation.<sup>9</sup>

This study aimed to assess the effects of physical training on myocardial structure, cardiac function, and exercise tolerance of Wistar rats, when exercise was performed after the time needed for the development of doxorubicin-induced cardiotoxicity.

## Materials and Methods

### General considerations

The research protocol was approved by the ethics committee on the use of animals (approval number 022/14). All procedures were carried out in accordance with the Guide for the Care and Use of Laboratory Animals and with the Ethical Principles in Animal Experimentation of the National Council for the Control of Animal Experimentation.

Thirty young adult male Wistar rats (about eight weeks old) from our animal experimentation laboratory were used and the sample was for convenience. The initial weight of the animals was approximately 250 g/animal. The environmental conditions for all groups were the same regarding temperature (25 °C), relative humidity, noise, and light/dark cycle (12h/12h). The animals receive food and water ad libitum.

### Experimental Design

#### Doxorubicin administration

The animals were randomly divided into four groups: control (C), exercise (EX), doxorubicin (DX),

and doxorubicin and exercise (DXEX). The DX and DXEX groups received intraperitoneal injections of doxorubicin hydrochloride (Fauldoxo – 25 mg/mL, Libbs Farmacêutica, Embú, São Paulo), three times per week for two weeks (six doses de 1.25 mg/kg) reaching a cumulative dose of 7.5 mg/kg,<sup>10</sup> and the C and EX groups received a 0.9% saline solution.

#### Physical training protocol

The physical training protocol started two weeks after the last doxorubicin injection. The EX and DXEX groups animals went through an initial adaptation period during which they got in contact with water at a temperature of  $32 \pm 2$  °C for 30 minutes during one week.<sup>11</sup>

The animals performed swimming with an additional load of 5% of body weight. The rats were placed in a tank with a water column height, corresponding to 150% of their body length.<sup>12</sup> The water temperature was maintained at  $32 \pm 2$  °C to be thermally neutral in relation to the rats' body temperature.<sup>13,14</sup> Physical training was carried out for four weeks, with three swimming sessions per week. To increase the workload, a small vest with lead weights was placed around the anterior region of the trunk. The load was adjusted weekly according to changes in the animals' body weight. During the experimental period, the C and DX groups were also placed in contact with water at a temperature of  $32 \pm 2$  °C, following a protocol similar to that of animals in training. Table 1 shows the periodization of physical training.

#### Echocardiography

The echocardiogram was performed 24 hours after the exercise tolerance test at the end of the experimental period. For the echocardiographic images, we intraperitoneally administered a combination of ketamine (Ketamine 10%, Agener União Química Farmacêutica Nacional S/A, Embu-Guaçu, SP, Brazil, 74 mg/kg) and xylazine (Dopaser, Laboratories Calier S/A, Barcelona, Spain, 8 mg/kg) for the maintenance of spontaneous breathing during examination. After anesthesia, the anterior chest was shaved.

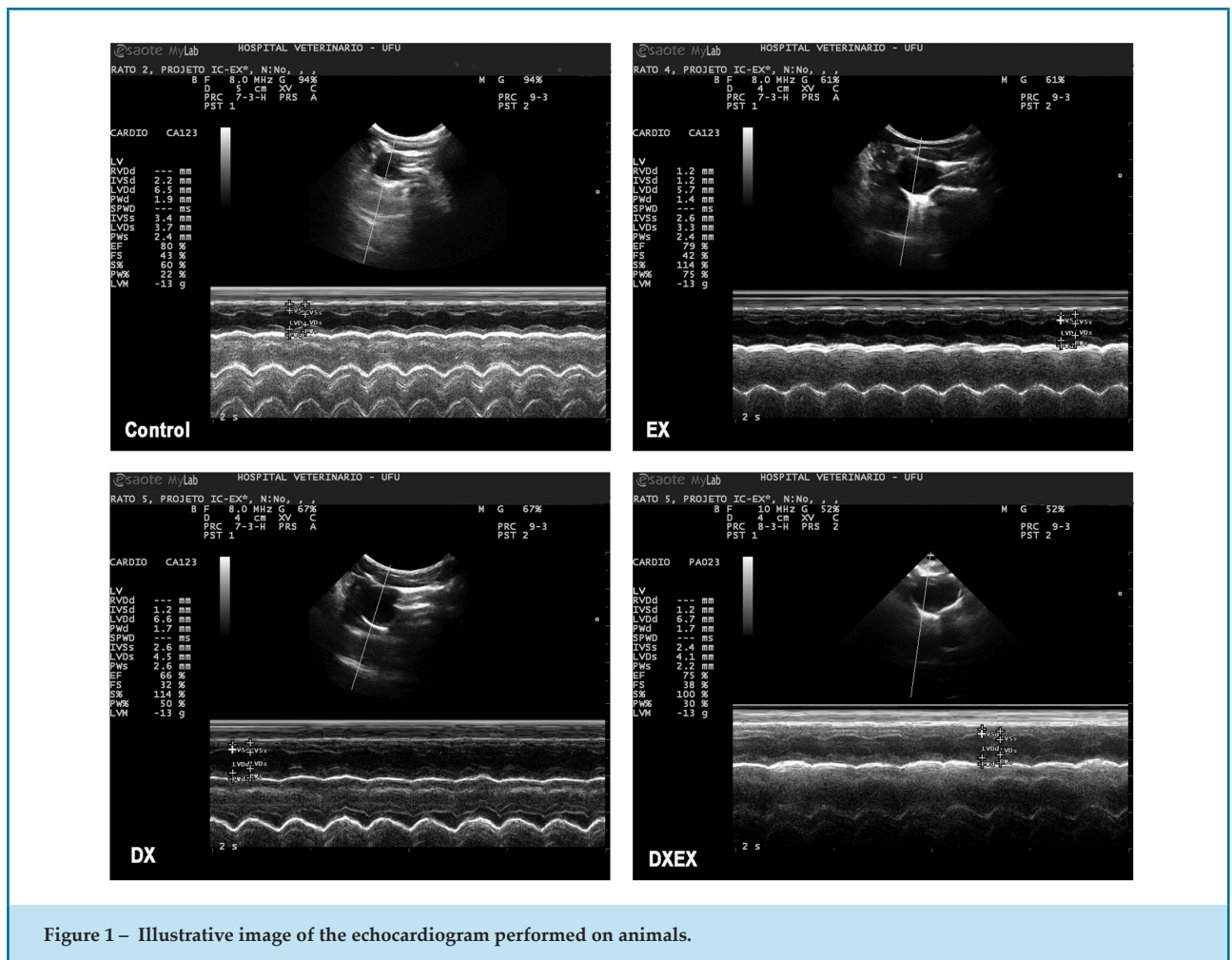
Echocardiography was performed using the ESAOTE equipment, model MyLab VET 30 Gold, which generated images in unidimensional and bidimensional modes. We used a section transducer with a frequency of 8 Mhz, depth of 3.0 cm, and section angle of 75°. In the M mode, in the right parasternal cross-sectional view

of the tendinous cords, the diameter of the left ventricle was measured during diastole and systole to calculate the fractional shortening (FS) using the equation:  $FS\% = [(LVEDD-LVESD)/LVEDD] \times 100$ , where LVEDD is the left ventricular end-diastolic diameter and LVESD is the left ventricular end-systolic diameter. In the same

view, left ventricular diastolic and systolic volumes (LVDV and LVSV, respectively) were measured using the Teichholz<sup>15</sup> method to calculate the left ventricular ejection fraction (LVEF) using the formula  $LVEF = [(LVDV-LVSV)/LVDV] \times 100$ . Heart rate was measured during echocardiography (Figure 1).

**Table 1 – Periodization of animals' physical training**

Training weeks	Load (% of body weight)	Training time per day of the week (min)		
		Monday	Wednesday	Friday
1st	5%	10	15	15
2nd	5%	20	25	25
3rd	5%	30	35	35
4th	5%	40	40	40



**Figure 1 – Illustrative image of the echocardiogram performed on animals.**

## Statistical Analysis

Quantitative data were presented as mean and standard deviation or median. Data residuals were not normally distributed (tested with Kolmogorov-Smirnov test) and did not have homoscedasticity (tested with Levene test). For this reason, we used generalized linear models,<sup>16</sup> since we were able to choose the most appropriate probability distribution according to the Akaike's criterion and data type. We adopted a complete factorial design method, using exercise-related factors (levels: yes or no), the use of doxorubicin (levels: yes or no), and their interaction. To evaluate heart weight, heart weight/body weight, LVEF, and SF, we used the Gamma distribution with logarithmic link function. For assessment of body weight, diastolic diameter of the left ventricle, and systolic diameter of the left ventricle, we used the Gaussian distribution with the identity link function. The distribution function was selected according to the Akaike's criterion, or a lower value among the distributions tested. To evaluate heart rate and exercise tolerance, we used the Poisson distribution with the logarithmic link function, since the values were positive integers. When treatments differed between or within factors, the means were compared in pairs using the LSD (Least Significant Difference) test. All analyses were conducted using the SPz 20.0 GLzM module (SPSS, Inc., Chicago, IL, USA). The significance level was set at 0.05 (p-value <0.05).

## Results

### General state of the animals, mortality, and macroscopic aspects of hearts

After the first three doses of doxorubicin, as compared with untreated animals, treated animals had piloerection, yellow hair, exudation around the eyes and nostrils, and reduced physical activity.

The survival rate of the animals that received the accumulated dose of 7.5 mg/kg of doxorubicin was 97.5%.

During material collection, the hearts of treated animals were more flaccid and collapsed on the examination plate, reproducing one of the macroscopic characteristics described in dilated cardiomyopathy.

### Evolution of body weight and heart weight

Tables 2, 3 e 4 show the results of body weight, heart weight, and the ratio of heart weight to body weight of animals after treatment. Animals treated with doxorubicin had lower body weight compared to non-treated animals. Heart weight and the ratio of heart weight to body weight in the EX group were higher than in the other groups.

**Table 2 – Chi-square statistics and p-values from generalized linear models applied for analysis of the data and their respective distribution**

Trait (unit)	Chi-square (p-value)			
	Doxorubicin	Exercise	Interaction	Distribution
ET (min)	0.32 (0.572)	101.42 (<0.001)	5.35 (0.021)	Poisson
HR (bpm)	0.10 (0.747)	4.56 (0.033)	11.98 (0.001)	Poisson
LVEDD (mm)	1.08 (0.901)	0.02 (0.901)	2.12 (0.145)	Gaussian
LVESD (mm)	2.38 (0.123)	1.09 (0.297)	3.53 (0.060)	Gaussian
LVEF (%)	3.53 (0.060)	3.26 (0.071)	3.82 (0.051)	Gamma
SF (%)	2.41 (0.121)	2.66 (0.103)	3.52 (0.060)	Gamma
Heart weight (g)	4.53 (0.033)	5.63 (0.018)	7.43 (0.006)	Gamma
Body weight (g)	4.03 (0.045)	1.35 (0.244)	0.23 (0.628)	Gaussian
HW/BW Ratio (%)	2.95 (0.086)	4.40 (0.036)	6.62 (0.010)	Gamma

ET: exercise tolerance; HW/BW: heart weight/body weight ratio; HR: heart rate; LVDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LVEF: left ventricular ejection fraction; SF: shortening fraction.

**Table 3 – Exercise tolerance, heart rate, left ventricular end-diastolic diameter and end-systolic diameter, ejection fraction and shortening fraction, heart weight, body weight, and heart weight/body weight ratio in animals in the control, exercise, doxorubicin, and doxorubicin plus exercise groups at the end of the experiment; values in mean ± standard deviation (median)**

Trait (unit)	Treatment (n)			
	Control (n = 3)	Exercise (n = 3)	Doxorubicin (n = 3)	Doxorubicin plus Exercise (n = 3)
ET (min)	18.43 ± 18.62 (8)	44.80 ± 21.24 (60) *	20.89 ± 17.91 (18) †	36.44 ± 19.46 (31) *†‡
HR (bpm)	337.67 ± 117.36 (286)	280.67 ± 26.41 (286) *	298.00 ± 83.07 (262) *	311.33 ± 130.00 (255) †
LVEDD (mm)	5.70 ± 0.75 (5.6)	6.23 ± 0.21 (6.3)	6.70 ± 1.15 (7.1)	6.07 ± 0.97 (6.3)
LVESD (mm)	3.37 ± 0.67 (3.7)	3.70 ± 0.60 (3.7)	4.73 ± 0.81 (5.1) *	3.57 ± 1.18 (4.2) ‡
LVEF (%)	77.33 ± 9.29 (80)	76.67 ± 9.07 (78)	62.00 ± 2.65 (63) *†	77.00 ± 13.11 (75) ‡
SF (%)	41.67 ± 8.08 (43)	40.67 ± 8.50 (41)	29.67 ± 1.53 (30) *†	42.00 ± 12.77 (39) ‡
	Control (n = 5)	Exercise (n = 3)	Doxorubicin (n = 9)	Doxorubicin plus Exercise (n = 9)
Heart weight (g)	0.90 ± 0.08 (0.9)	1.50 ± 1.06 (1.0) *	0.96 ± 0.20 (0.9) †	0.92 ± 0.12 (0.9) †
Body weight (g)	347.71 ± 19.34 (356.0)	360.40 ± 18.72 (356.0)	336.00 ± 15.71 (336.0)	341.22 ± 29.47 (328.0)
HW/BW (%)	0.26 ± 0.03 (0.26)	0.43 ± 0.33 (0.26) *	0.28 ± 0.06 (0.28) †	0.27 ± 0.03 (0.28) †

ET: exercise tolerance; HW/BW: heart weight/body weight ratio; HR: heart rate; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LVEF: left ventricular ejection fraction; SF: shortening fraction; \* p-value < 0.05 vs. control, † p-value < 0.05 vs. exercise, ‡ p-value < 0.05 vs. doxorubicin: based on the significant minor differences (due to marginal effects, the variables LVESD, SF and LVEF showed significant differences in pair comparisons, regardless of the non-significant interaction).

## Echocardiography

Assessment of the anatomy of the cardiac chambers revealed that the LVESD of the DX group was increased compared to the C and DXEX groups. The LVEDD did not differ between the groups. Analysis of the systolic function of the left ventricle was made based on the SF and LVEF values. SF and LVEF in the DX group were lower when compared to C, EX, and DXEX, and LVEF in the DXEX group was similar to that of the C. Heart rate in EX was lower than that of C and DXEX. Echocardiographic results are described in Tables 2, 3 and 4.

## Exercise tolerance test

Exercise tolerance in the EX group was higher than in the other groups. The DXEX group showed greater tolerance to effort when compared to the DX and C groups (Tables 2, 3 and 4).

## Discussion

Our study showed that physical training initiated after the onset of doxorubicin-induced cardiotoxicity,

improved cardiac function and exercise tolerance in rats.

Cardiotoxicity caused by doxorubicin is cumulative and dose-dependent,<sup>17-19</sup> and can progress to heart failure of variable severity.<sup>20</sup> Macroscopic and functional cardiac changes, caused by chemotherapy and found in the present study have been described in other animal experimental models<sup>21,22</sup> and are similar to those reported in humans.<sup>23</sup> These changes indicate that the treatment intervention triggered cardiac toxicity, and can be used as an experimental evaluation of various therapies.

Systemic reactions reflect the toxicity induced by doxorubicin. In our experiments, we observed lower weight gain, reduced physical activity, and exudation around the eyes and nostrils. These reactions may interfere with organic metabolic processes and are more intense when higher doses of chemotherapy are administered.<sup>22</sup>

Physical training is part of the non-pharmacological treatment of acute and chronic heart failure,<sup>24</sup> and is recommended by the Brazilian Cardio-Oncology Guidelines. Current evidence indicates that physical

**Table 4 – Main factor effect of the exercise tolerance test, heart rate, left ventricular end- diastolic diameter and end systolic diameter, ejection fraction and shortening fraction, heart weight, body weight, and heart weight/body weight ratio in animals in the control, exercise, doxorubicin and doxorubicin plus exercise groups at the end of the experimente; values in mean  $\pm$  standard deviation (median)**

Trait (unit)	Main factor			
	Exercise		Doxorubicin	
	Yes (n = 6)	No (n = 6)	Yes (n = 6)	No (n = 6)
ET (min)	39.43 $\pm$ 19.73 (34)	19.81 $\pm$ 17.65 (14)	28.67 $\pm$ 19.83 (26.5)	29.42 $\pm$ 23.18 (23.5)
HR (bpm)	296.00 $\pm$ 85.56 (270.5)	317.83 $\pm$ 93.50 (274)	304.67 $\pm$ 97.85 (258.5)	309.17 $\pm$ 82.24 (286)
LVDD (mm)	6.15 $\pm$ 0.63 (6.3)	6.20 $\pm$ 1.03 (6.05)	6.38 $\pm$ 1.01 (6.6)	5.97 $\pm$ 0.58 (6.15)
LVSD (mm)	3.63 $\pm$ 0.84 (3.95)	4.05 $\pm$ 1.00 (3.8)	4.15 $\pm$ 1.11 (4.25)	3.53 $\pm$ 0.60 (3.7)
LVEF (%)	76.83 $\pm$ 10.09 (76.5)	69.67 $\pm$ 10.39 (65.5)	69.50 $\pm$ 11.79 (64.5)	77.00 $\pm$ 8.22 (79)
SF (%)	41.33 $\pm$ 9.73 (40)	35.67 $\pm$ 8.38 (32)	35.83 $\pm$ 10.57 (31)	41.17 $\pm$ 7.44 (42)
	Yes (n = 14)	No (n = 16)	Yes (n = 18)	No (n = 12)
Heart weight (g)	1.13 $\pm$ 0.66 (0.9)	0.93 $\pm$ 0.16 (0.9)	0.94 $\pm$ 0.16 (0.9)	1.15 $\pm$ 0.71 (0.9)
Body weight (g)	348.07 $\pm$ 27.07 (352.5)	341.13 $\pm$ 17.81 (343.5)	338.61 $\pm$ 23.06 (333.0)*	353.00 $\pm$ 19.34 (356.0)*
Ratio HW/BW (%)	0.33 $\pm$ 0.20 (0.28)	0.27 $\pm$ 0.05 (0.27)	0.28 $\pm$ 0.05 (0.28)	0.33 $\pm$ 0.22 (0.26)

ET: exercise tolerance; HW/BW: heart weight/body weight ratio; HR: heart rate; LVDD: left ventricular end-diastolic diameter; LVSD: left ventricular end-systolic diameter; LVEF: left ventricular ejection fraction; SF: shortening fraction; \* p-value < 0.05 yes vs. no use of doxorubicin, based on the significant minor differences.

training plays both preventive and therapeutic roles for heart disease in patients who will receive chemotherapy.<sup>7</sup>

Two questions motivated this study. The first one is when to start physical training, and the second one is whether exercise can reverse the cardiotoxic effects.

To answer these questions, first we need to validate the methodology used, since the clinical identification of cardiac dysfunction in animals is not always easy. One of the difficulties of interpreting results of models of doxorubicin-induced cardiomyopathy is to quantify the intensity of cardiac dysfunction in relation to the dose of chemotherapy administered in the experiment. Identifying heart failure and its clinical manifestations in animal experiments is a challenge in this context. However, based on the echocardiographic findings, we can affirm that cardiotoxicity did occur in our experiment.

The reduced left ventricular systolic function found in our study was associated with the intensity of cardiotoxicity. Changes in the diameter of cardiac

chambers, observed in the DX group, may arise in response to interacting factors, such as inflammation, apoptosis of cardiomyocytes, compensatory cell hypertrophy, fibrosis, and damage caused to the complex mechanism of activation and coupling/uncoupling of contractile filaments.<sup>25</sup>

The echocardiographic findings answer the question regarding the potential of physical exercise to reverse cardiotoxic effects, and point out two aspects. One of them concerns the hemodynamic repercussion and its potential consequences in cardiac remodeling processes. In experimental models, the simplest way to identify remodeling is to measure the heart weight and calculate the ratio between heart weight and animal weight. These two variables were greater in the EX group compared to C, which corroborates the occurrence of cardiac hypertrophy in response to regular physical training.<sup>26</sup> However, when rats trained in the presence of doxorubicin (DXEX group), these variables did not increase, showing that chemotherapy in some way interrupted the hypertrophic signaling triggered by physical

exercise. The echocardiographic measurements of the left ventricular diameters (LVESD and LVEDD) confirmed this finding, since they did not change in the DXEX group compared to C.

Physical exercise acts in cardiac remodeling and thereby plays role in preventing and treating heart failure in patients with preserved, partially preserved or reduced LVEF.<sup>27</sup> Cardiovascular changes induced by physical activity include blood pressure reduction, improvement of autonomic modulation, enlargement of ventricular cavity dimensions, and increase in stroke volume, contributing to physiological cardiomyocyte hypertrophy with reduced cardiac fibrosis.<sup>28</sup> Additional beneficial effects of exercise include increased antioxidant activity, decrease in the release of reactive oxygen species and pro-apoptotic signaling, and a reduction in myocyte turnover (by suppressing pro-apoptotic protein synthesis), leading to favorable changes in energy metabolism.<sup>29</sup>

These mechanisms may have improved exercise tolerance in the DXEX group when compared to the DX group in our study. The importance of these effects derives from the fact that doxorubicin-induced cardiotoxicity and cardiac dysfunction reduce exercise tolerance, worsen the prognosis, and increase morbidity and mortality.<sup>30</sup>

In addition to central cardiovascular factors, improved skeletal muscle metabolism in response to physical training may increase exercise tolerance during cancer treatment.<sup>31</sup> An improved skeletal muscle metabolism improves endothelial function, and increases muscles' oxidative capacity, the percentage of type I skeletal muscle fibers (oxidative), the recruitment of motor units, and capillary density.

Short and long-term exposure to antineoplastic agents may also cause autonomic dysfunction with direct effects on the cardiovascular system, such as increased cardiac chronotropism and impaired conduction through the atrioventricular node.<sup>32</sup>

The present study showed that four weeks of aerobic training initiated after the development of doxorubicin-induced cardiotoxicity preserved systolic function, increased their exercise tolerance, and effectively adapted resting heart rates in rats. The maximum heart rate achieved during an exercise test with the same workload is lower in individuals who had undergone physical training.<sup>33</sup> This reduction has been shown in both animals and humans and been attributed to greater

vagal stimulation and lower sympathetic activity.<sup>34-36</sup> This neurohumoral modulation of physical training has a favorable impact on functional capacity.<sup>34</sup> However, we need to be careful in interpreting these data. Although the standard deviation found in the C was very high, it is unlikely that it could have been influenced by this random response.

The mechanisms involved in the improvement of cardiotoxic effects by exercise are complex and multifactorial, so an early detection of cardiotoxicity is important to develop strategies to prevent or minimize its deleterious effects.

### Study Limitations

Our study has limitations related to the methodology used to assess changes in right and left ventricular function. The use of tissue Doppler and the analysis of regional and global longitudinal strain would be more sensitive to detect small changes in ventricular function that precede the drop in ejection fraction and its recovery. Furthermore, the analysis of plasma biochemical markers such as troponins and brain natriuretic peptide, not performed in this study, may be useful in detecting early cardiotoxicity.

### Conclusion

Physical training initiated after the onset of doxorubicin-induced cardiotoxicity improved left ventricular function and exercise tolerance in Wistar rats.

### Author contributions

Conception and design of the research: Souza FR, Resende ES; Acquisition of data: Souza FR, Campos EC, Gonçalves DLN, Mantovani MM, Duarte PRA; Analysis and interpretation of the data: Souza FR, Campos EC, Lopes LTP, Gonçalves DLN, Beletti ME, Duarte PRA, Resende ES; Statistical analysis: Rodrigues CM; Obtaining financing: Souza FR, Resende ES; Writing of the manuscript: Souza FR; Critical revision of the manuscript for intellectual content: Campos EC, Gonçalves A, Resende ES.

### Potential Conflict of Interest

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

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## Study Association

This article is part of the thesis of Doctoral submitted by Fernanda Rodrigues de Souza, from Federal University of Uberlândia.

## Ethics approval and consent to participate

This study was approved by the Ethics Committee on Animal Experiments of the Ethics Commission on Use of Animals (CEUA) under the protocol number 022.

## Erratum

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