ORIGINAL ARTICLE

Protective Effects of Accumulated Aerobic Exercise in Infarcted Old Rats

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Abstract

Background: Aerobic exercise exerts cardioprotective effects on myocardial infarction. However, there is lack of information about the possible protective effects of continuous or accumulated aerobic exercise performed prior to myocardial infarction in aging.

Objective: To evaluate the preventive effects of continuous or accumulated aerobic exercise on physical capacity, pulmonary congestion and ventricular weight in rats submitted to myocardial infarction.

Methods: Old male Wistar rats were divided into four groups: sham control, sedentary infarcted, continuous aerobic exercise submitted to myocardial infarction, and accumulated aerobic exercise submitted to myocardial infarction. Body weight and maximum speed were evaluated at the beginning and at the end of the protocol. Trained groups performed continuous (1 h a day) or accumulated (30 minutes in the morning and 30 minutes in the afternoon) exercise. All groups, except the sham control, were submitted to myocardial infarction surgery at the end of the protocol. Heart, skeletal muscles, as well as wet and dry lung were weighed. The significance level in statistical analysis was established at $p < 0.05$.

Results: Both continuous and accumulated exercise caused an increase in physical capacity in rats, as well as prevented its further impairment after myocardial infarction, and in the accumulated exercise group this prevention was greater. The continuous exercise group demonstrated an increase in lung water content, while the accumulated exercise group presented a reduction in body weight and an increase in left ventricle relative weight.

Conclusion: In conclusion, the data of the present study indicate that accumulated aerobic exercise present a better protective effect than continuous aerobic training in the context of myocardial infarction and aging. (Int J Cardiovasc Sci. 2018;31(5)505-512)

Keywords: Myocardial Infarction/prevention & control; Exercise; Physical Endurance; Aging; Rats.

Introduction

Myocardial infarction (MI) is one of the leading causes of death worldwide. Its pathophysiology consists of myocardial cell death due to prolonged ischemia resulting from the occlusion of coronary artery ramification. After MI, a process of ventricular remodeling is initiated, in which cardiac changes - such as ventricular dilatation - accompanied by increased sympathetic activity occur as compensatory mechanisms that, at the beginning, regulate survival but, over time, worsen the prognosis of the infarcted patient.[1,2] In aging, due to changes such as stiffening of the arteries, which in turn results in increased afterload on the left ventricle, systolic blood pressure and changes in the left ventricular wall, the elderly are more susceptible to develop cardiovascular diseases, such as MI.[3,4]

In this sense, physical training has been used as an important strategy in the management of cardiovascular diseases, due to its several benefits, such as reduction of adiposity and increased heart rate variability, thus contributing to prevent cardiac events.[5] However, if a

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cardiac event does occur, the vascular, neurohumoral and cardiopulmonary adaptations from exercise are effective in attenuating cardiometabolic complications and minimizing the deleterious effects of ischemia.[6] Experimentally, it has been shown that moderate intensity aerobic training prior to MI attenuates cardiac dysfunction and deterioration promoted by ischemia and preserves the contractile properties of cardiomyocytes,[7] as well as attenuates the loss of physical capacity and autonomic cardiac dysfunction.[8]

One of the recommended ways to perform physical activity is accumulated aerobic training, which consists of performing the exercise in bouts over the course of a day,[9,10] and represents an interesting approach for individuals who have little time in their daily lives, as well as for the elderly.[11] This type of training can increase adherence to physical activity and, consequently, the number of people who follow the recommendations for physical exercise.[12]

However, there is lack of knowledge concerning the possible protective effects of continuous or accumulated exercise performed prior to MI in aged rats. Thus, the aim of the present study was to evaluate the preventive effects of continuous and accumulated aerobic exercise on physical capacity, pulmonary congestion and ventricular weight in rats submitted to MI.

Material and methods

Experiments were performed in old male Wistar rats (24 months; ~475g), from the Animal House of the São Judas Tadeu University, São Paulo, Brazil. Rats were fed standard laboratory chow and water ad libitum. Rats were housed in collective polycarbonate cages, in a temperature-controlled room (22°C) under a 12h dark–light cycle (lights on 07:00 - 19:00 hours). The experimental protocol was approved by the Institutional Animal Care and Use Committee of the São Judas Tadeu University and the study was conducted in accordance with the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publication number 96-23, revised 1996).

The experimental design can be observed in Figure 1. At the beginning of the protocol, rats were assigned by simple random distribution to four groups, in which the sample size was defined by convenience: sham control (C, n = 6); sedentary infarcted (S, n = 5); continuous aerobic exercise submitted to MI (CE, n = 6), and accumulated aerobic exercise submitted to MI (AE, n = 7). All experiments are described below in detail; however, in summary, groups were adapted to the treadmill and submitted to a maximal treadmill exercise test (MTET) to determine aerobic capacity and exercise training intensity. Trained animals - CE and AE - were submitted to aerobic exercise protocols for 1 month,[13] whereas sedentary groups - C and S - were placed on the stationary treadmill at least three times a week to provide a similar environment. Twenty-four hours after the last session of exercise, or in a relative period for the sedentary groups, animals were underwent to MI (i.e., S, CE, and AE) or sham (i.e., C) surgeries. 1 day after MI, the animals were again submitted to the MTET. Four days after MI,[8] the animals were killed by decapitation in order to remove the organs.

Maximal exercise test and aerobic exercise training

Approximately one month before MI or sham surgeries, sedentary and trained rats were adapted to the treadmill (10 minutes per day; 0.3 km/h) for four days. All animals were submitted to a MTET to determine aerobic capacity and exercise training intensity at the beginning of the protocol, after aerobic ET protocol and post myocardial infarction. These evaluations were conducted by a blinded observer. MTET was based on a ramp protocol, which consisted of treadmill exercise with 0.3 km/h increments every 3 minutes, and finished when the animals were not able to run. Our group previously demonstrated that MTET could detect differences in aerobic performance; since that, the maximal running speed achieved in the test has presented a good correlation with the maximum oxygen consumption.[14]

After the adaptation period, the sedentary groups (i.e., C and S) underwent exercise only during the maximum running test. However, the animals were placed on the stationary treadmill at least three times a week to provide a similar environment. Aerobic training was performed on a motor treadmill (Inbramed TK-01, Brazil) at low intensity (30% of maximum running speed on MTET). Nevertheless, CE group performed the training on a continuous form for 1 h a day, while the AE group performed cumulatively (30 minutes during the morning – 8:00-9:00 a.m. and 30 minutes during the afternoon – 16:00-17:00 p.m.). Both trainings were conducted 5 days a week for 4 weeks.

Myocardial infarction

Twenty-four hours after the last session of exercise, or in a relative period for the sedentary groups,

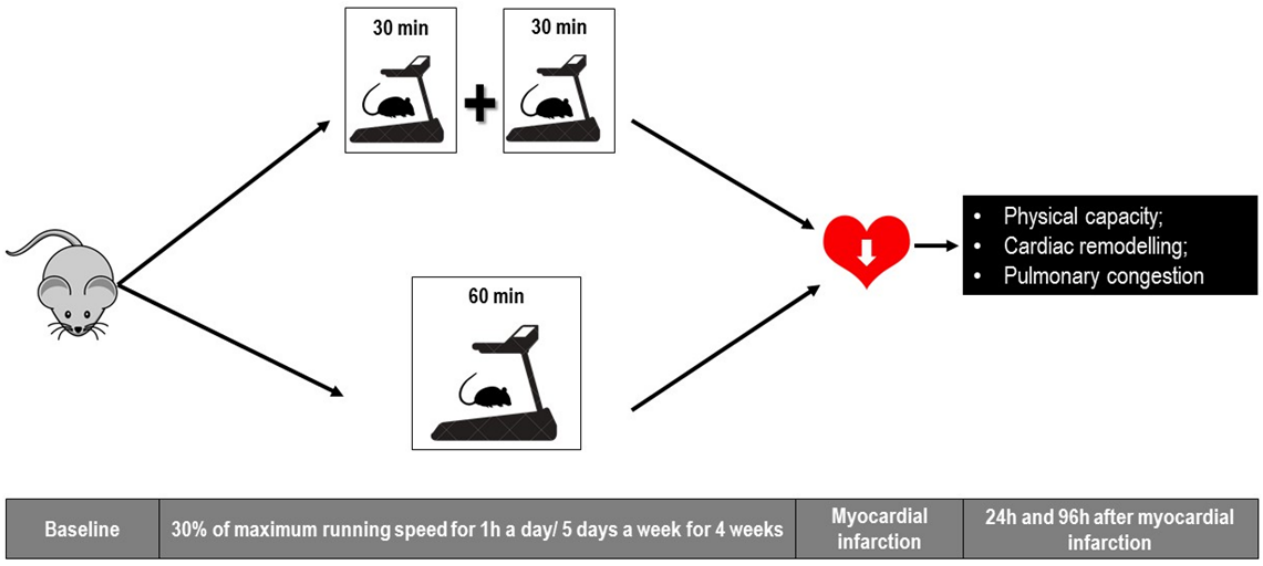

Figure 1 - Experimental design of the current study.

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 described previously.[8] 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 (Sham surgery). The chest was closed with a silk suture.

Lung water content

The lungs were removed and weighed (wet weight) and then placed in an oven for 24 hours at 80ºC. Posteriorly, the lungs were weighed again (dry weight). The water content (%H_2O) of each lung was defined by the equation: % H_2O = (wet weight - dry weight) / wet weight x 100.[15]

Organ and muscles relative weight

The left ventricle (LV), right ventricle (RV), soleus and gastrocnemius were removed and weighed. The calculation of the organs relative weight of each rat was performed dividing the weight of each organ (in grams) by the body weight of each animal, and multiplying the result by 100. The result was then expressed in grams/100 grams of live weight (g/100 g l.w.).[16]

Statistical analyses

Statistical analyses were performed with GraphPad Prism software (Version 7.0 for Windows; GraphPad Software, Inc., San Diego, CA). 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 posttest. Statistical differences between the data measured over time were assessed using repeated-measures ANOVA. All tests were two-sided and the significance level was established at $p < 0.05$.

Results

At the beginning of the protocol, MTET indicated that physical capacity was similar in all groups (C = 0.9 ± 0.0 km/h; S = 0.8 ± 0.11 km/h; CE = 0.9 ± 0.09 km/h; AE = 0.9 ± 0.04 km/h). However, after the experimental protocol, CE and AE groups demonstrated higher MTET in comparison with the initial assessment (CE: +55%; AE: +33%), C group (CE: +100%; AE: +71%) and S group

(CE: +100%; AE: +71%). No further differences were observed among exercised groups. At post MI moment, CE group, but not AE, showed reduced physical capacity in comparison with the final assessment (after the last session of ET) (-35%). Nevertheless, MTET values of both trained groups were still higher (100%) in relation with the S group (100%) (Figure 2).

Regarding the morphological parameters, body weight was similar among all groups in the beginning of the protocol (~475g). However, after MI, AE group demonstrated significant reduction on body weight in relation to the initial assessment (Figure 3).

On the other hand, organ analysis demonstrated increased LV relative weight in AE. There were no further significant differences between the groups in relation to RV, soleus and gastrocnemius relative weight (Table 1).

Figure 4 shows the results of lung water content, an index of pulmonary congestion, in all groups. Data demonstrated a slight, but significant, increase in pulmonary congestion in CE in relation to all the other groups.

Discussion

The main findings of the present study are that aerobic training, regardless of the arrangement of the program - continuously or fractioned -, causes significant increase on physical capacity of elderly rats, as well as acts protecting against further impairments caused by MI injuries. However, an interesting phenomenon was observed after MI, since CE showed decreased exercise capacity in comparison with the time before MI, as well an elevated index of pulmonary congestion. On the other hand, both parameters were still stable in the AE group, which might indicate a superior protective effect of this kind of intervention in relation to the continuous ET program.

Regarding the physical capacity before MI, the data of the present study are in line with most evidence in the literature from animal[17,18] and human studies,[12,19,20] since both trained groups showed increased aerobic capacity after ET (CE: +55%; AE: +33%). However, data have demonstrated inconsistent results regarding the magnitude of the increase after the protocols, so that is possible to observe evidence indicating more favorable results towards continuous protocols,[17,19] whereas others showed highest levels of physical capacity after accumulated aerobic training.[20] In the current study, accumulated and continuous aerobic training propitiated similar improvement on physical capacity. The inconsistencies among these findings could be a

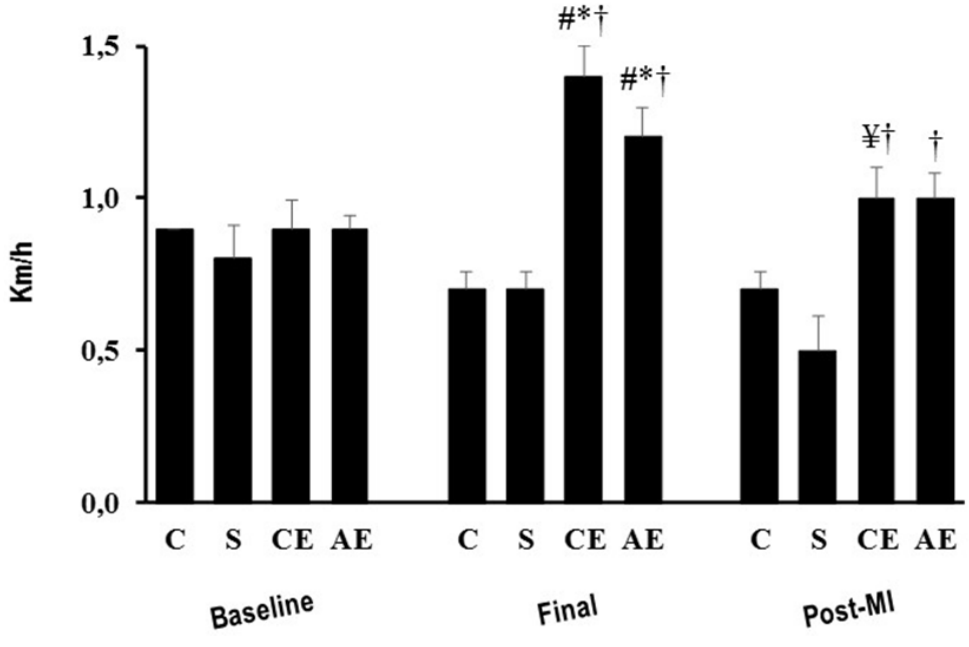

Figure 2 - Maximal treadmill exercise test in control (C), infarcted sedentary (S), continuous exercise (CE) and accumulated exercise (AE) groups. Values expressed as mean ± SEM. #p < 0.05 vs. Baseline; ¥p < 0.05 vs. Final; *p < 0.05 vs. C; †p < 0.05 vs. S.

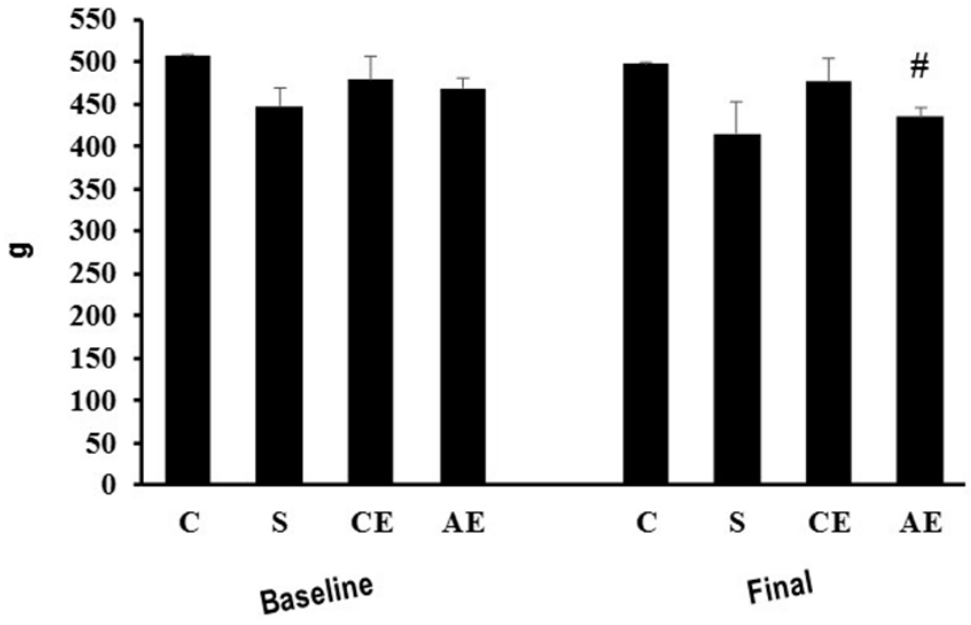

Figure 3 - Body weight in control (C), infarcted sedentary (S), continuous exercise (CE) and accumulated exercise (AE) groups. Values expressed as mean ± SEM. #p < 0.05 vs. Baseline.

Table 1 - Organ and muscles relative weight in control (C), infarcted sedentary (S), continuous exercise (CE) and accumulated exercise (AE) groups

	C	S	CE	AE
LV (g/100 g l.w.)	0.206 ± 0.002	0.253 ± 0.009	0.257 ± 0.010	0.276 ± 0.017*
RV (g/100 g l.w.)	0.064 ± 0.012	0.056 ± 0.001	0.056 ± 0.001	0.061 ± 0.006
Soleus (g/100 g l.w.)	0.028 ± 0.003	0.035 ± 0.003	0.032 ± 0.002	0.035 ± 0.001
Gastrocnemius (g/100 g l.w.)	0.338 ± 0.03	0.362 ± 0.059	0.371 ± 0.029	0.388 ± 0.039

*Values expressed as mean ± SEM. LV: left ventricle; RV: right ventricle. *p < 0.05 vs. C.*

function of the differences in the design of exercise program and sample types. Indeed, when Martinez et al.[17] underwent Wistar rats to a moderate-intensity aerobic exercise protocol similar with the ET that was used in the current study, the researchers observed a similar magnitude of improvements among the groups.

Interestingly, after MI, both groups demonstrated a two-fold increase on physical capacity in relation to the S group. However, this evaluation was significantly decreased in CE when it was compared with the time before MI, whereas no significant alterations were observed in CE. Furthermore, CE demonstrated a higher index of pulmonary congestion - lung water content - in comparison with all other experimental groups. These data suggest that elderly rats trained through continuous aerobic training might present decreased capacity to cope with MI injury in relation to elderly rats trained through aerobic fractioned exercise.

Decreased physical capacity in S is widely described in the literature. Indeed, after MI, cardiorespiratory fitness is commonly decreased due to a central mechanism - characterized by decreased cardiac output, which is the product of cardiomyocyte death and, consequently, impaired cardiac function and unwanted cardiac remodeling - and a peripheral mechanism - caused by marked alterations on skeletal muscle architecture (i.e.,

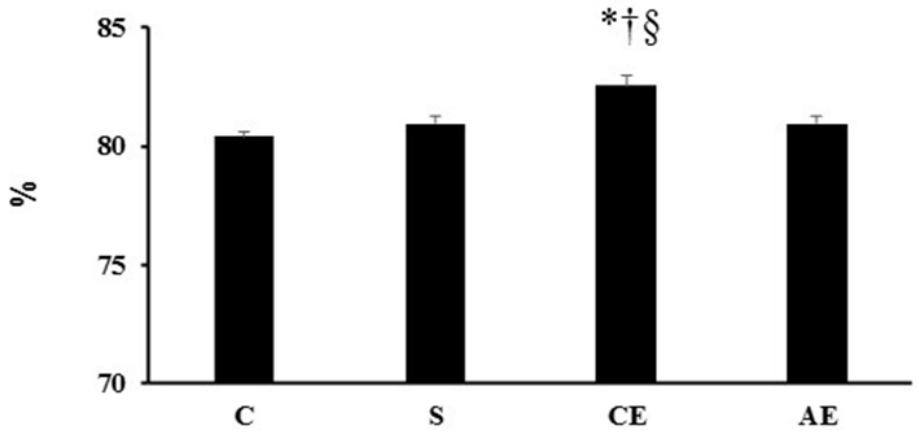

Figure 4 - Lung water content in control (C), infarcted sedentary (S), continuous exercise (CE) and accumulated exercise (AE) groups. Values expressed as mean ± SEM. *p < 0.05 vs. C; †p < 0.05 vs. S; §p < 0.05 vs. AE.

atrophy) and function (e.g., impaired metabolism), which may collaborate with the development of the myopathy observed during heart failure.[18,21,22,23] Regarding the preserved capacity demonstrated by both trained groups, our data are in line with evidence that have demonstrated that adult rats underwent to exercise training programs previous to MI showed increased cardiorespiratory fitness in comparison with sedentary groups.[8]

However, as aforementioned, the CE group demonstrated a phenomenon that was not described before in the literature, indicating that older rats submitted to surgical induction of MI might show decreased aerobic capacity associated with pulmonary congestion. These controversial results are probably a product of the animal used in the current study. In fact, most studies have studied adult animals and, for the first time, the protective effect of exercise training was investigated in older animals.

The plausibility behind this theory is based on the decreased capacity of the old organic system to cope with stressful agents (e.g., physical, chemical), as postulated by Fransceschi et al.[24] in the inflammaging metatheory. This possibility has been confirmed by several experiments, including the recent data from El Assar et al.[25] that indicated that frail older adults present a low expression of genes involved in the cellular response to stress (i.e., oxidative stress and cellular hypoxia). [25] In congruence, a phenomenon denominated as myocardial injury - which is characterized by a transient myocardial injury in the right ventricle (RV) - might be observed in response to aerobic exercise due to the greater hemodynamic load and wall stress.[26-28] In fact, animal and human studies have demonstrated impaired RV function, decreased cardiac handling, and increased cardiac biomarkers (i.e., creatine kinase and N-terminal pro-brain natriuretic peptide), during and immediately after the end of the aerobic exercise.[26-28]

Therefore, it is possible to infer that very-old adult rats present an impaired capacity to cope with the stressful environment developed in response to continuous aerobic exercise, leading to significant pulmonary congestion; thus, fractioned aerobic exercise seems to be a more beneficial recommendation for older adults, especially those with increased risk to develop cardiovascular diseases and frailty, since after an ischemic event they can present a better prognosis.

Although some limitations of the present study should be considered (e.g., the absence of echocardiographic evaluations to evaluate left ventricle dimensions and function) our observations suggest that the improvements observed after accumulated aerobic training may have occurred due to beneficial cardiac remodeling induced by the exercise training, as shown by the increased LV relative weight observed in AE. These data are supported by several evidences, which indicate a beneficial cardiac remodeling after exercise training due to increased LV cavity and dilation, inducing significant functional changes in cardiac contractility and, consequently, improving cardiac output.[29,30] Additionally, MI area was not evaluated and this is a limitation of the present study.

Conclusions

In conclusion, data of the present study are that aerobic training, regardless the arrangement of the program - continuously or fractioned -, causes significant increase on physical capacity of elderly rats, as well as acts protecting against further impairments caused by MI injuries. However, accumulated aerobic exercise seems to be a better approach once CE showed decreased exercise capacity in comparison with the time before MI, as well an elevated index of pulmonary congestion, whereas both parameters were stable in the AE group.

Author contributions

Conception and design of the research: Rodrigues B. Acquisition of data: Feriani DJ. Analysis and interpretation of the data: Feriani DJ, Coelho-Júnior HJ. Statistical analysis: Feriani DJ, Coelho-Júnior HJ. Obtaining financing: Rodrigues B. Writing of the manuscript: Feriani DJ, Coelho-Júnior HJ, Rodrigues B. Critical revision of the manuscript for intellectual content: Irigoyen MC, Rodrigues B.

Potential Conflict of Interest

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

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee on Animal Experiments of the Universidade São Judas Tadeu under the protocol number 008/2013.

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