High Intensity Physical Exercise before the Brain Ischemia Promotes Increase in Brain Injury

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Studies have demonstrated the beneficial effects of light- and moderate-intensity physical exercise on the nervous system of animals with cerebral ischemia. To investigate the effects of two high-intensity physical exercise protocols, standardized for resistance and strength gain, in rats trained before cerebral ischemia induced by Bilateral Common Carotid Artery Occlusion (BCCAO). Forty-eight male Wistar rats were divided into two groups: with ischemia and without ischemia (sham). Both groups were subdivided into animals that performed high-intensity exercises in the muscle strength modality (I+Ex2; Sham+Ex2; n=16); animals submitted to high-intensity exercises in the aerobic modality (I+Ex1; Sham+Ex1; n=16), and animals that did not practice physical exercises - sedentary (I+Sed; Sham+Sed, n=16). Cerebral ischemia was induced using the BCCAO model. The physical training program used before the procedure was of high intensity, in the aerobic and muscular strength modalities, and was performed using a vertical ladder, for 4 weeks, 5 days per week. In order to process and stain the brain tissue, the Nissl method was used for neuron labeling and quantification in the cortex, striatum, and hippocampus. As for the animals' body weight and the heart weight differences were found between the groups I+Ex2 and Sham+Ex2 ($p<0.05$). Data on neuron quantification in the cerebral cortex, dentate gyrus, and right and left striatum revealed significant differences between groups. High-intensity physical training in the strength gain modality promotes significant damage to the animal's brain when performed prior to BCCAO-induced cerebral ischemia.

Key Words: Brain ischemia—Exercise—Muscle strength—Endurance training—Neurons—Hypertrophy left ventricular—Cerebrovascular circulation—Neuroprotection

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Introduction

Stroke is a rapidly evolving vascular disorder in the brain that lasts more than 24 h and can lead to the death of the individual. This cerebrovascular alteration can be hemorrhagic or ischemic and causes significant motor, sensory, and cognitive changes, being considered one of the leading causes of mortality in the world.[1-3]

Due to the high level of comorbidities and mortality of this disease, it has become necessary to intervene in risk factors that can be modified and that can mitigate or prevent its occurrence. Physical exercise is a strong ally in the treatment and prevention of several cardiovascular, chronic, and cerebrovascular diseases.[4,5] However, it is important to highlight the ideal type of physical exercise, intensity, duration, and frequency of sessions for neuroprotection and recovery of brain injury areas.

Physical activity is considered any activity that involves an energy expenditure greater than the rest levels and physical training is when the movements are structured and planned, to disturb homeostasis and produce acute fatigue, which promotes the improvement of physical performance when combined with adequate recovery periods. To achieve fatigue and adaptations induced by physical exercise, it is necessary to change the intensity, duration and frequency, as they differentially modulate the molecular signaling in skeletal muscle.[6,7]

The maximum oxygen consumption rate (VO2max), as well as other physiological parameters, such as maximum heart rate (HRmax) are important to determine the intensity of exercise.[7,8]

According to De Lade et al.,[9] the high intensity resistance protocol is one that uses a VO2 max of 85-90%, lasting up to 40 min, with load change in the fourth week. Rezaei et al.[10] states that high intensity resistance exercises are those performed between 30 to 60 min with the maximum heart rate (HRmax) between 85-90%. Resistance exercise (ER), or strength, stands out for improving body composition, increasing protein synthesis, muscle strength, positively altering the lipid profile and promoting blood pressure adjustments, and, above all, increasing insulin sensitivity and glucose tolerance. These are exercises that require the realization of strength to perform the task, and the increase in the imposed loads happens gradually, with less repetitions and shorter time between sets. These are protocols that use 85-90% of VO2max. and HRmax, lasting up to 40 min and changing loads progressively in the first week.[11] On the other hand, high-intensity resistance exercises have more repetitions and less overload in sets.[10]

In studies with animals with cerebral ischemia that practiced physical exercises of moderate-intensity, neuronal proliferation and maturation was observed, as well as reduced activation of the pro-inflammatory cascade, improved vascular integrity,[12,13] increased production of brain-derived neurotrophic factors (BDNF) and the nerve growth factor (NGF), greater survival of neuronal cells,[14] decreased injuries in movement planning areas of the brain, and improved motor performance,[15]

In the study by Teixeira-Coelho et al.,[7] in which high-intensity physical training protocols were performed, a chronic elevation of glucocorticoids was noted due to excessive activation of neuroinflammation, with the release of pro-inflammatory cytokines, which alter both the structure and the functioning of neuronal cells. Kemi et al.[8] showed that animals submitted to high-intensity exercise presented significant increases in cardiac hypertrophy, cardiomyocyte contractility, Ca^{+2} transport, and physical fitness. Other authors reported an improvement in endothelial function and greater vascular adaptation when compared to animals that performed moderate-intensity exercises.[16]

Cardiac alterations should be considered in brain studies as they interfere with brain blood flow. According to Mill and Vassalo,[17] cardiac hypertrophy is an adaptive mechanism of the heart, as consequence of increased activity or overload and can occur in three different ways.

The standardization of the experimental model of disease induction in an animal model allows the reproduction of signs and symptoms that contribute to the identification of activation routes and investigations of possible treatments and interventions in this brain injury. The model of bilateral common carotid artery occlusion (BCCAO) makes it possible to mimic bilateral brain lesions with molecular and cellular changes in nervous tissue and thus reproduce bilateral symptoms.[18-20]

Studies investigating the effects of high-intensity exercise on the nervous system of animals with neurological diseases are still limited. From that study arose the need to investigate whether strength training is, in fact, harmful to the brain's nervous tissue and associate such impairment with the type of cardiac hypertrophy found.

Thus, the objective of the present study was to investigate the effects of two high-intensity physical training protocols, one for resistance gain and the other for strength gain, in rats trained before BCCAO-induced cerebral ischemia.

Material and methods

Study animals

Forty-eight male Wistar rats (*Rattus norvegicus*, var. *albinus*) were kept in polypropylene cages with free access to water and feed, a 12-h light/dark photoperiod, room temperature between 21°C and 22°C, and relative air humidity of 60-70%.

The sample size was calculated based on the analysis of the standard deviation, the level of significance (usually between 0.05 and 0.01), and the power of the test (generally between 80% and 90%) and was statistically defined as 8 rats per group.[22]

The animals were divided into six groups (8 rats each), totaling 48 animals, and were weighed at the beginning of the experiment, during every day physical training, and before (72 days) and after (75 days) the surgical procedure. All conducted procedures followed Brazilian ethical standards, recommendations from the International Animal Protection Standards, and the Brazilian Code of Animal Experimentation.[23] This study was submitted to the Ethics Committee Involving the Use of Animals (ECIUA) of the Federal University of São João del-Rei and was approved under protocol No. 023/2018.

Twenty-four animals were submitted to ischemia via BCCAO and distributed at random (Table 1) in the following subgroups: I+Ex1 (ischemia+exercise-1, n=8): high-intensity training protocol – aerobic modality,[24] prior to surgery; I+Ex2 (ischemia+exercise-2, n=8): high-intensity training protocol – muscle strength gain modality,[25] prior to surgery; and I+Sed (ischemia+sedentary, n=8): did not perform previous exercise. The other twenty-four animals (Sham) underwent the surgical procedure, but not BCCAO, and were distributed in the following subgroups: Sham+Ex1 (sham+exercise-1, n=8): high-intensity training protocol – aerobic modality,[24] prior to surgery; Sham+Ex2 (sham+exercise-2, n=8): high-intensity training protocol – muscle strength gain modality;[25] and Sham +Sed (sham+sedentary, n=8): did not perform previous exercise.

Physical training

The high-intensity physical training was carried out on the vertical ladder, following the modified protocol used in the study by Peixinho-Pena et al.,[25] using a ladder that was 110cm long and 18 cm wide, and had an 80° inclination. The housing box at the top end of the stairs was 20 cm high, 20 cm wide, and had 20 cm of housing sectors.

The animals were allocated into two exercise protocols: 1 and 2. Initially, they underwent a 3-day period of adaptation to the ladder prior to the start of training, where they made three attempts per day, without any weight load. The rats were placed in the housing chamber for 60 s in order to familiarize themselves with the safe environment. In the first attempt, the animals remained at a distance of 35 cm from the chamber; in the second attempt, at 55 cm; and in the third attempt, at 110 cm.

After the adaptation period, the rats from the group that underwent the high-intensity training protocol, aerobic modality,[24] defined as exercise group 1, were submitted to exercise on the ladder for 4 weeks, 5 days a week, with a mean duration of 90 min per session. In this training protocol, an HRmax was used 80-95% where more repetitions of exercises were performed and gradual increase in weight load in sessions. The training protocol proposed by Hornberger and Farrar (24) was modified on account of cardiorespiratory system adaptations, emphasizing aerobic capacity, with more repetitions and lower weight loads in each series. This training protocol was carried out as follows: eight series of climbing, including 8 to 12 repeated movements (upward climbing) in each series to reach the housing chamber, in the first, second, and third week, totaling 64 climbs. In the fourth week, the rats performed six series of 8 climbs using 90% weight loads, totaling 48 climbs, and four series of 6 climbs using 100% weight loads, totaling 24 climbs. In the first week of training, the animals were exercised with a load equivalent to 15% of their body weight. Meanwhile, in the second week, the load was changed to 25% of the animal's total weight, and in the third, 50%. In the fourth week, the animals were trained with a 75% body weight load during the first two days, a 90% weight load for the next two days, and on the last day, with a load of 100% of the animal's body weight (Fig. 1). The changes in weight load always occurred on Mondays of the 1st, 2nd, and 3rd week, providing an adequate resting period and modifications in stimuli intensity. The animals climbed upward approximately 64 times in each training session (day).

Table 1. *Evaluation of heart weight (A), body weight (B) and the heart/body weight ratio (C) among groups.*

Group	Mean	Standard Error	Significance P	Group	Mean	Standard Error	Significance P
A)				**B)**			
I+Ex2	1.2000	0.082887	0.0498	I+Ex2	314,25	7.8325	0.0270
Sham+Ex2	1.0415	0.14423		Sham+Ex2	327,25	12.756	
I+Ex1	1.2840	0.11562		I+Ex1	343,00	9.3427	
Sham+Ex1	1.4227	0.11210		Sham+Ex1	364,44	8.9242	
I+Sed	1.0740	0.053742		I+Sed	339,78	12.322	
Sham+Sed	1.0740	0.053742		Sham+Sed	361,25	15.870	
C)							
I+Ex2	227.25	2.7108	0.0001				
Sham+Ex2	337.17	18.017	0.0003				
I+Ex1	250.84	10.661	0.049				
Sham+Ex1	263.32	11.738					
I+Sed	311.45	7.9802					
Sham+Sed	326.75	21.047					

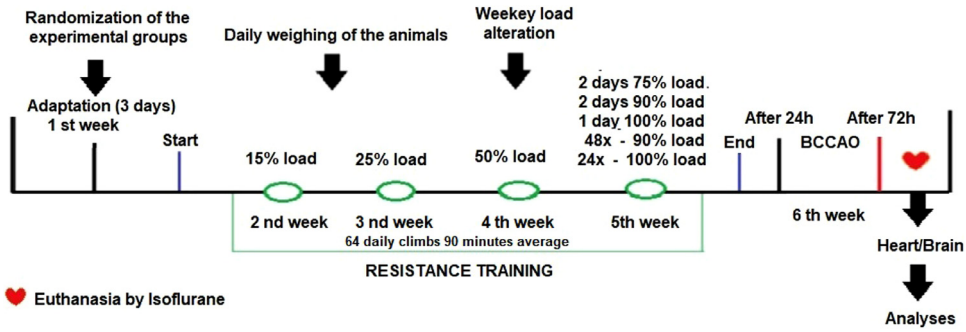

Fig. 1. *Experimental design of the resistance training protocol.*

Exercise group 2, which was submitted to high-intensity training, muscle strength gain modality (25), also underwent the adaptation period and exercised during 4 weeks, 5 days a week, with a mean duration of 45 min per session. The strength training consisted of eight series of climbing, involving 8 to 12 repeated movements in each series, to reach the housing chamber. In this training protocol, an HRmax was used 80-95% where less repetition of exercises and greater weight loads were performed for muscle strength gain training. On the first day of training, the animals were submitted to progressive weight loads: the first two climbs with a load of 50% of the animal's total body weight; the third and fourth with a load of 75% body weight; the fifth and sixth with a load of 90% body weight; and the last two climbs with a load of 100% of the animal's total body weight (Fig. 2). An additional load of 10 g was added to each training session whenever the 100% animal body weight load was easily overcome. The animals climbed upward approximately 8 times in each training session (day).

The interval between series was 60 s for the animal to rest in the housing chamber. The weight load was attached to the proximal portion of the animal's tail, 3 cm from its caudal root. It had a cylindrical shape and a total length of 16 cm and was secured with a woolen thread surrounded by adhesive rubber tape adjusted to protect the animal's skin.[24-26]

Although the VO_2 max of the animals in the present assessment were not measured, the intensity levels of the used protocols were based on previous studies, where it was estimated that high levels of intensity are those performed with VO_2 max. above 80%.[27,28] The protocols used herein ensure such energy consumption by the animal.[24-26]

The maximum heart rate (Contec 08a-vet Multiparameter Veterinary Monitor) was considered for the calculation of the intensity of the physical training where it was considered a training that used HRmax. 80-95%.[9,10]

Bilateral common carotid artery occlusion (BCCAO)

The model of bilateral common carotid artery occlusion (OACCB) makes it possible to mimic bilateral brain lesions with molecular and cellular changes in nervous tissue and thus reproduce bilateral symptoms.[18-20]

In order to conduct the BCCAO, the animals were anesthetized with xylazine (5mg/kg; intramuscular) and ketamine (50mg/kg; intraperitoneal). The preparation for the surgical procedure was performed by trichotomy and antisepsis of the ventral cervical region, with a median sagittal incision of approximately 3 cm in length. The tissues were dissected until the exposure of the left common carotid artery (CCA), which was isolated using a nylon thread and clamped simultaneously with the right CCA using bulldog forceps, causing cerebral ischemia for 15 min.[29]

After 15 min, the forceps were carefully removed to avoid damaging the carotid arteries, allowing brain tissue reperfusion.[18] Upon surgical procedure completion, the tissues of the anterior cervical region were sutured using Nylon (3.0) thread and a triangular curved needle. The animals recovered in the polypropylene cages, with body temperatures between 36-38°C and water and feed *ad libitum*.[30]

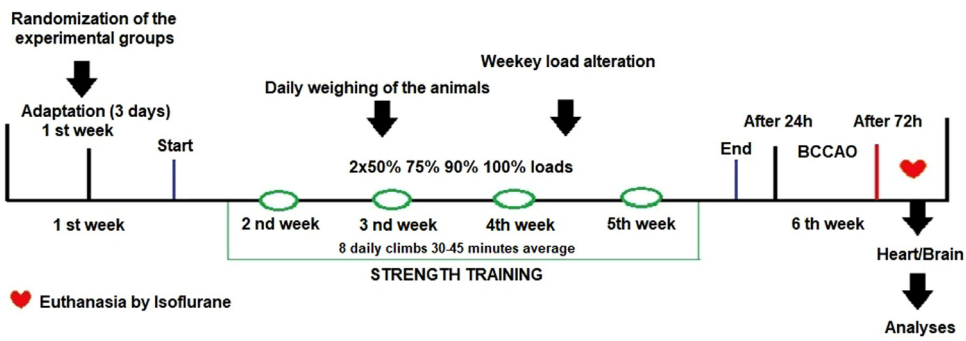

Fig. 2. *Experimental design of the strength training protocol.*

Histopathological analysis and neuronal tissue quantification

At the end of the experiment (81 days), the animals were euthanized by isoflurane inhalation and decapitation. The brain was removed through occipital craniotomy and the heart by median sternotomy.

The collected brains were cleaved in 1-mm sections in the coronal plane, followed by fixation in 10% neutral formalin-buffered solution for 24 h and later dehydration in successive solutions of alcohol. After diaphanization in xylol, the sections were impregnated and included in paraffin, according to the standard histological processing protocol. The paraffin blocks were sectioned using a microtome, in which 5 μm-thick cuts were obtained, and the histological sections were stained by the Nissl method for neuronal cell counting.[15,31] This technique consists of immersing the slide into a cresyl violet solution to evidence neuron cytoplasms and Nissl corpuscles. In neuronal injury, these corpuscles may disappear, a phenomenon known as chromatolysis. Thus, this form of staining serves as an indicator of neuronal viability.

The quantification of neurons in the two cerebral hemispheres, namely the region of the cortex, the dentate gyrus, and the right and left striatum, was performed using the following locations in relation to the bregma point: Section 3.20 mm, at the edge of the motor cortex region with ischemia; and section -2.80 mm, the region of the dentate gyrus apex (hippocampus). These areas were analyzed due to their importance in the regulation and planning of motor control in animals.[21] During neuron quantification, conducted in the predefined area of 7.30 × 5.47 inches (640 × 480), using the Image J-Pro Plus software (Media Cybernetics Inc., MD, USA), version 4.5, for Windows 10, only neurons with Nissl corpuscles in their cytoplasm were considered. Three images of each histological section were taken, totaling 18 images from each animal and 144 from each group. The imaging software Motic Images Plus 2.0 and a digital camera (Moticam 580) were attached to the microscope (Motic), and a 400× magnification was used. Next, the selected images were analyzed with the aid of the Image J software.[32]

Macroscopic analysis of the heart

In the macroscopic analysis of the heart, the organ's relative weight was measured in relation to the animal's body weight (heart weight ÷ animal weight x 100%).

In order to calculate the thickness and diameter of the left ventricle (LV), cuts were made in the lower 1/3 of each LV for ventricular hypertrophy analysis, after fixation of the hearts in 10% formaldehyde. Afterward, the LVs were cross-sectioned at the midpoint of the distance between the apex and the coronary groove of the heart (1/3) to measure the two parameters.[33]

Images of the heart sections were taken with a digital camera (Sony Xperia Z5, 23MP resolution), and the LV diameter and thickness were measured using the Image J-Pro Plus Software.[34]

Statistical analysis

Data analyses were performed using the GraphPad Prism 5.0 statistical program and the one-way analysis of variance (ANOVA) statistical test, followed by Tukey's post-hoc test. For the analysis of the averages of neurons in the cortex, striatum and dentate gyrus, the two-way analysis of variance (ANOVA) was used, followed by the Newman-Keuls post-test, considering a level of significance of $p<0.05$. The results were expressed as mean ± standard error of the mean (SEM).

Results

Animal body weight, heart weight, and heart/body weight ratio

The results regarding heart weight and body weight did present significant differences between groups I+Ex2 and Sham+Ex2. When analyzing the heart/body weight ratio, significant differences between groups were evidenced ($p<0.0001$), as shown in Table 1.

Macroscopic Analysis of the Heart

The data from the macroscopic analysis of the heart revealed no significant difference between groups regarding the thickness of the LV ($p=0.8576$). On the other hand, the LV diameter analysis indicated a significant difference between groups ($p<0.0001$), as shown in Table 2.

Neuron quantification

Cortex

The data obtained after neuron quantification in the right and left cerebral cortex showed significant differences between groups, as evidenced in Table 3 and Fig. 3.

Dentate gyrus

When comparing the mean neuron counts in the dentate gyrus of the hippocampus of the right and left cerebral hemispheres, significant differences were also found between groups (Table 4 and Fig. 4).

Striatum

The results obtained from the neuron quantification in the right and left striatum showed significant differences between groups (Table 5 and Fig. 5).

Discussion

When analyzing the data on the animals' body weight was observed significant differences were observed among groups I+Ex2 and Sham+Ex2. In the study by Canakc et al.,[35] carried out with 30 Sprague Dawley rats, in which the induction of cerebral

Table 2. *Evaluation of the thickness of the left ventricle (A) and ventricular diameter (B).*

Group	Mean	Standard Error	Significance P	Group	Mean	Standard Error	Significance P
A)				**B)**			
I+Ex2	52.875	3.4818	0.8576	I+Ex2	299343	9745.1	0.0001
Sham+Ex2	53.375	2.5630		Sham+Ex2	299659	9990.3	0.0021
I+Ex1	50.625	3.3538		I+Ex1	320009	13341	0.049
Sham+Ex1	58.444	3.5595		Sham+Ex1	384776	9793.0	
I+Sed	62.111	3.7433		I+Sed	439242	6541.2	
Sham+Sed	52.625	2.7800		Sham+Sed	385160	27601	

Table 3. *Evaluation of the number of neurons among groups in the right cerebral cortex (A) and left cerebral cortex (B).*

Group	Mean	Standard Error	Significance P	Group	Mean	Standard Error	Significance P
A)				**B)**			
I+Sed	56.875	3.7485	0.0001	I+Sed	41.250	2.9565	0.0001
Sham+Sed	59.500	0.94491	0.0019	Sham+Sed	41.250	2.9565	
I+Ex1	44.000	1.5236		I+Ex1	19.500	1.6583	
Sham+Ex1	44.000	1.5236		Sham+Ex1	52.750	3.6388	
I+Ex2	21.125	1.8071		I+Ex2	52.750	3.6388	
Sham+Ex2	53.625	3.7509		Sham+Ex2	84.750	3.9258	

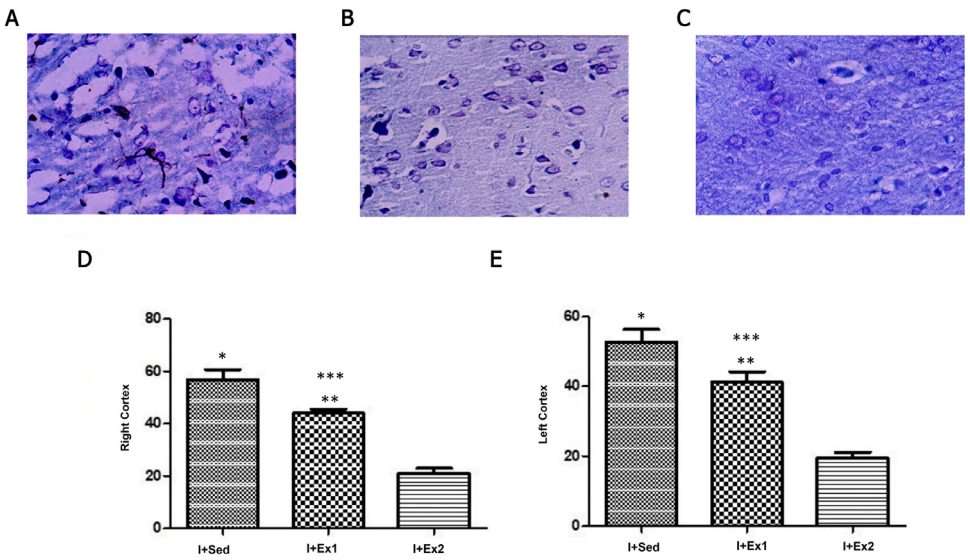

Fig. 3. *Photomicrograph of the histological section of the right and left cortex stained with cresyl violet of groups I+Sed (A), I+Ex1 (B), and I+Ex2 (C), and triple analysis (D, E). 400 × magnification. The bars represent the mean and the central columns indicate the standard error of the mean (ANOVA) of the ischemic groups. (D, E) *p<0.001 in relation to I+Ex2, **I+Ex2, *** I+Sed.*

ischemia was performed using the right common carotid artery occlusion (RCCAO) model described no changes in the animals' body weight. Meanwhile, in their research, Parkkinen et al.[36] reported that the surgical procedures performed to induce cerebral ischemia caused weight loss in all animals, although subsequent recovery was observed.

Regarding heart weight, the highest and lowest means were observed in the I+Ex2 and Sham+Ex1 groups, respectively. Considering the heart/body weight ratio, group I+Ex2 presented the lowest means when compared to the other groups, whereas the Sham+Ex2 group had the highest means. These data corroborate with the study by Damázio et al.,[21] where it was evidenced that the

Table 4. *Evaluation of the number of neurons among groups in the right dentate gyrus (A) and left dentate gyrus (B).*

Group	Mean	Standard Error	Significance P	Group	Mean	Standard Error	Significance P
A)				**B)**			
I+Sed	127.000	8.0178	0.0001	I+Sed	123.00	9.3216	0.0001
Sham+Sed	173.88	3.7580		Sham+Sed	161.63	5.8765	
I+Ex1	131.63	4.7281		I+Ex1	139.00	8.8277	
Sham+Ex1	131.63	4.7281		Sham+Ex1	139.00	8.8277	
I+Ex2	38.625	5.3650		I+Ex2	42.000	46790	
Sham+Ex2	127.00	8.0178		Sham+Ex2	123.000	9.3216	

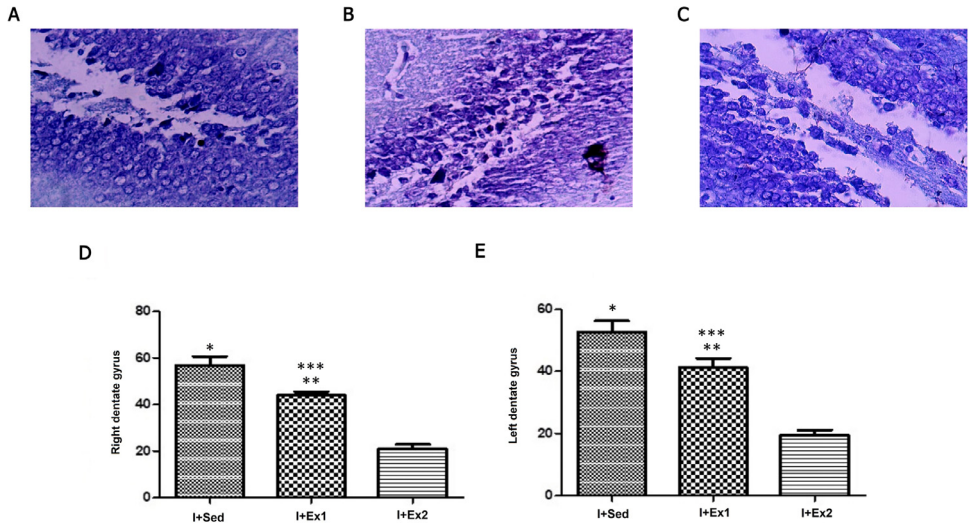

Fig. 4. *Photomicrograph of the histological section of the dentate gyrus stained with cresyl violet of groups I+Sed (A), I+Ex1 (B), and I+Ex2 (C), and triple analysis (D, E). 400 × magnification. The bars represent the mean and the central columns indicate the standard error of the mean (ANOVA) among the ischemic groups. (D, E) *p<0.001 in relation to I+Ex2, **I+Ex2, ***I+Sed.*

group submitted to high-intensity training in the muscle strength gain modality also presented lower heart/body weight mean ratios.

The results indicate that there was a change in concentric cardiac hypertrophy in the group of animals that performed high-intensity exercise with muscle strength gain. Such hypertrophy, associated with the decrease in LV diameter, suggests that there might have been an increase in the ejection strength of blood to the cerebral arteries.

As for the data on neuron quantification in the animals' cerebral cortex, lower means were observed in both the right and left cerebral hemispheres in the I+Ex2 group, while higher means were noted in the sedentary and Sham+Ex2 groups. In the dentate gyrus of the hippocampus and the right and left striatum, the lowest mean was found in the I+Ex2 group, whereas the highest means were observed in the sedentary groups and the animals submitted to high-intensity resistance training (I+Ex1).

The results obtained in this study suggest that high-intensity physical training in the form of muscle strength gain promoted significant damage to the animals' brain when performed before BCCAO-induced cerebral ischemia. The cardiac changes observed in this group may have generated changes in blood flow to the brain, causing an increase in the area of brain damage. Although strength training is indicated in the guidelines for rehabilitation of patients with cerebral ischemia after brain injury, there are still no well-defined protocols that consider the intensity, frequency, series and ideal repetitions.[37] In the present study, it was evidenced that high intensity training in the modality of muscle strength gain when performed before the ischemic event can generate permanent damage to the brain of rats.

The group of animals that performed high-intensity exercise in the aerobic modality presented higher mean neuron counts in the brain areas analyzed, indicating that this exercise modality may benefit the nervous tissue in animals with cerebral ischemia due to BCCAO. These data corroborate with the study Rezaei et al. (10), where animals that performed high-intensity exercises lasting 30 and 60 min exhibited a lower volume of cerebral infarction and a greater amount of angiogenesis markers in the striatum. Moderate aerobic exercise, carried out for longer periods and repeated before a stroke, can improve

Table 5. *Evaluation of the number of neurons present in the right striatum (A) and left striatum (B).*

Group	Mean	Standard Error	Significance P	Group	Mean	Standard Error	Significance P
A)				**B)**			
I+Sed	39.000	4.9929	0,0001	I+Sed	42.000	3.8266	0.0001
Sham+Sed	47.500	2.1381		Sham+Sed	48.125	0.8959	
I+Ex1	46.875	3.1250		I+Ex1	47.125	3.6715	
Sham+Ex1	46.875	3.1250		Sham+Ex1	47.125	3.6715	
I+Ex2	18.000	2.1297		I+Ex2	19.000	1.5698	
Sham+Ex2	39.000	4.9929		Sham+Ex2	42.000	3.8266	

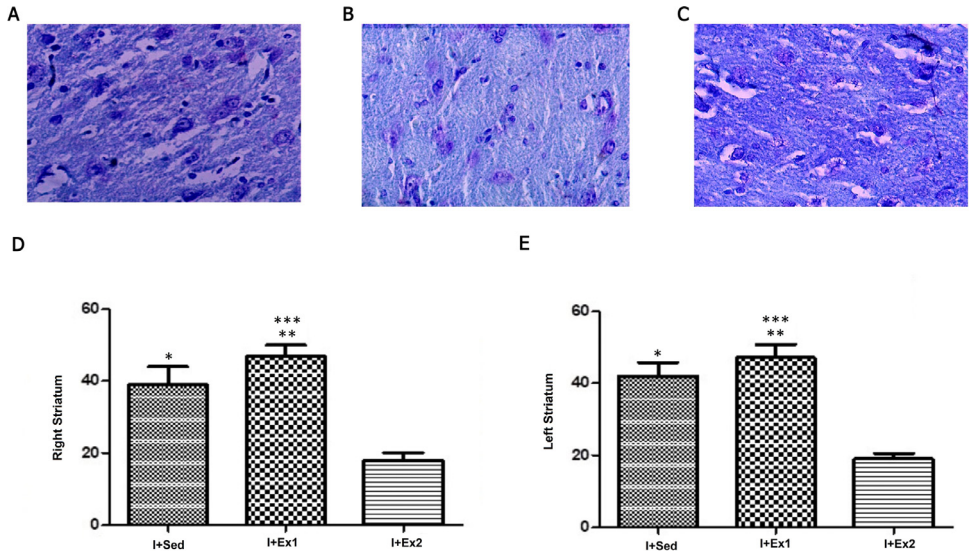

Fig. 5. *Photomicrograph of the histological section of the striatum stained with cresyl violet of groups I+Sed (A), I+Ex1 (B), and I+Ex2 (C), and triple analysis (D, E). 400 × magnification. The bars represent the mean and the central columns indicate the standard error of the mean (ANOVA) among the ischemic groups. (D, E) *p<0.001 in relation to I+Ex2, **I+Ex2, ***I+Sed.*

neurological function when performed 3 to 4 days a week for 40 min.[38]

Vascularization is crucial for the recovery of cerebral ischemia, and physical activity maintains cerebrovascular integrity during reperfusion. Arrick et al.[39] demonstrated that treadmill exercises for 5 days during 8 weeks reduced the level of infarction after middle cerebral artery occlusion (MCAO) and improved vascularization in cerebral arterioles. Additionally, Woitke et al.[40] showed that after running exercises and MCAO, neurogenesis occurred in the hippocampus, with improvement in behavioral tests.

Thus, the present study evidenced that high-intensity physical exercise in the muscle strength gain modality decreases the diameter of the animals' LV. It may also have contributed to causing hemodynamic changes in the blood flow to the brain and triggered the most significant brain damage in the animals with BCCAO-induced cerebral ischemia.

It is noteworthy that the obtained results were found in animals. Nonetheless, this information may be useful for future studies in humans that investigate the higher incidence of cerebral ischemia in individuals who undergo high-intensity physical training programs before eventual episodes of cerebral ischemia. These data could raise awareness regarding the clinical complications that these types of training may develop in individuals with a genetic predisposition, family history, or risk factors for cerebral ischemia.

Conclusion

High-intensity physical training in the muscle strength gain modality promotes significant damage to the animal's brain when performed before BCCAO-induced cerebral ischemia. This form of exercise decreases the diameter of the animals' LV and may have caused an increase in ventricular pressure, thus increasing brain damage.

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