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Cardiac Structural Repercussions Induced by Exhaustive Physical Training in the Animal Model

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Abstract

The levels of physical activity (PA), as well as their intensity, are major impactors to achieve the full benefits of such practice. Exhaustive physical training (EPT) may be associated with the projection of structural damage to the heart muscle. Thus, the objective of the experimental study in the animal model, was to analyse how demanding training is related to structural changes in cardiomyocyte tissue. Sample of 15 male WISTAR rats at 04 weeks of age were randomly assigned to 02 groups: Sedentary (SED n = 5) and trained (TR n = 10) who were subdivided into a 1-week training (TR1 n = 5) and week (TR3 n = 5). The TR animals practiced running on a treadmill (-25º; 30m / minute; 60 min whose intensity increased 1.25 meters/ minute in each training session 6x / week for 03 weeks. The animals of the TR subgroup were sacrificed at the end of the first week (TR1 n = 5) and at the end of the third week (TR3 n = 5). For the inferential analysis, ANOVA was used and the data with non-normal distribution were then analysed with Kruskal-Wallis with a significance level of 5 % for macrophage M2, there was a significance between SED and TR1 with p = 0.0096, supposed to be a harmful process to the cardiac tissue due to excessive exposure. In the case of the M1 macrophage, significant differences were found in every period of training, meaning a picture of inflammation and interaction with adaptive immunity. The eccentric exercise practiced during the first three weeks induced cellular responses to stress stimuli in the cardiac tissue, maintaining the interaction of adaptive immunity. Potential benefits from the metabolic point of view, public health efforts should also focus on maintaining levels of physical activity since our study showed that intense physical activity had harmful effects at the cardiac level.

Keyword: *Physical training, damage, cardiomyocytes, rats.*

Introduction

The promotion of physical exercise has been strongly encouraged by the government, since physical activity has been identified as the main non-pharmacological agent, assuming a beneficial and protective role, especially at the physical, psychological and physiological level (1) (2).

The activity levels of physical activity (PA) as well as its intensity are large impactors order to reach the fullness of the benefits come and such practice. It is known that the level of AP practice is a relevant factor for maintaining good health (3) and this benefit is widely achieved with its regularity (4). Such practice and regularity may require repetitive exposure to the muscle, attributed by muscle contractions associated with greater mechanical tension, resulting in more severe, strenuous and exhausting exercise- induced muscle damage (5).

Exhaustive physical training (EPT) can be associated with the projection of damage to the muscular system, increasing the risk of excessive use of osteoarticular structures, culminating in overload injuries, fractures and fatigue (6)(7). For the system immunologic, all demand may suppress immunity and increase the risk of infection (8) and when associated with growth factors and reproductive

endocrine system level, the damage is even more harmful (9). For the cardiovascular system, it most likely reflects damage to cells, promoting structural changes in the myocardium due to loss of integrity of the desmosome connections (10) (11) (12) (13).

Structural damage to the cardiac muscle is evidenced by the increase in the various serological markers that include cardiac troponin I, creatine kinase and myocardial creatine kinase band, myoglobin and BNP, and these findings are characterized as myocardial injury, which causes an intense myocardial injury debate on the possible negative health consequences (14) (15).

Another tool for diagnosing damage to myocardial cells after demanding exercise is the echocardiography, making it possible to perform functional and structural measurements non-invasive detailed heart. Studies with endurance athletes have observed that during the development of cardiac adaptations, a series of structural changes occurred, including increased cardiac thickness and mass, increased left ventricular volumes, increased left atrial size, and increased aortic stiffness that suggest that part of this remodelling can be pathological, and not entirely benign and adaptive (16) (14).

As the electrocardiogram know that there is growing evidence that atrial fibrillation (AF) which is the most common cardiac arrhythmia, can ha occur in young athletes or middle-aged and healthy, and this condition is commonly associated with major cardiovascular diseases and structural damage to the heart muscle, causing permanent injuries associated with EPT (17). Another study with veteran athletes, evidenced that the exercise of chronic resistance, excessive, sustained and of high intensity, may be associated with a substrate for atrial and ventricular arrhythmias. With recurrent myocardial injury and repair, it may ha be associated with diastolic dysfunction and eventually result in irregular myocardial fibrosis (15).

We observe the practice of demanding exercises to improve performance and maintain health, which, over time, may denote harm instead of benefits. Although a certain amount of muscle damage may be necessary for muscle adaptation, excessive damage or inadequate recovery due to the short pause between EPT increases the risks in perspective with other benefits (18).

So is the fact that most studies suggest that the benefits of exercise physic the increase progressively with increasing physical activity and exercise training are beneficial, but it is possible that prolonged exercise and exercise training may adversely affect cardiac function in some individuals (19) (20) (21). However, few studies have examined the effects of the damage of demanding exercise on chronic repercussions at the cardiac level.

To this end, it is well established that biochemical, electrocardiogram and echocardiographic abnormalities are commonly observed transiently after the completion of EPT in athletes, although their clinical significance is unknown (18) (22) (23) (24), but cannot perform the analyses on your cardiac structure. Thus, the objective of the experimental study in the animal model, was to analyse how demanding training is related to structural changes in cardiomyocyte tissue. Such evidence will assist in the process to address the current gaps in our knowledge in this scenario to minimize the consequences of diseases and may suggest intervention strategies for the adoption and maintenance of physical activity, with emphasis on proposals for adherence to physical exercises on public health.

Material and Method

The present study had a sample of 15 male WISTAR rats (Charles River Laboratories Barcelona) at 4 weeks of age. The animals were housed in collective cages (2 per cage) with controlled temperature and humidity (22 ± 2ºC and 60 ± 10%) and 12 hours inverted light / dark with access to food and water *ad libitum.*

After one week of acclimatization, the rats were randomly assigned to 02 groups : Sedentary (SED n = 5) and trained (TR n = 10) that were subdivided into 01 week (TR1 n = 5) and 03-week training (TR3 n = 5). The TR animals practiced running on a treadmill (-25º; 30m/minute; 60 min whose intensity increased 1.25 meters/minute in each training session, reaching a maximum intensity at the end of the first and third weeks) 6x/week, during 01 and 03 weeks respectively

with eccentric contraction exercise due to mechanical demand and inflammatory response from intense physical exercise (25).

The animals of the TR subgroup were sacrificed at the end of the first week (TR1 n = 5) and at the end of the third week (TR3 n = 5). The SED animals remained limited to the space of the cage throughout the study and were sacrificed one day after the first week of the protocol. For sacrifice, the animals were weighed and anesthetized with ketamine (90 mg/kg, Merial, France), xylazine (10 mg/kg, Bayer, German) and sacrificed by exsanguination and the cardiac tissue collected and processed for structural analysis by optical microscopy and immunohistochemistry.

The processing of the tissues took place from the histological routines of the research laboratory and after the processing of the tissues, they were cut to 5µm thick and stained with haematoxylin-eosin (26) for analysis of muscle damage through the signs of cell degeneration necrosis, the presence of an inflammatory reaction and the degree of tissue disorganization (27) and also for the quantification of the cross-sectional area through analysis of round cells with nucleus in the center. Picrosirius Red staining (28) was used to analyse the collagen content and preparations for immunohistochemistry in the study of macrophage polarization (M1 and M2 activation), expression of kappa B nuclear factor (NF-kB) p65 and cell proliferation (KI 67).

The sections were analysed with an optical microscope (Axio Imager A1, Carl Zeiss; Germany) and the images recorded with a coupled digital camera (Leica DM4000B, Nussloch, Germany). A total of 150 photos were analyzed, 50 for each group, 10 for each animal in each subscript technique.

The data were tabulated using EXCEL for WINDOWS® and the data analysis was performed using the GraphPad Prisma® version 8 program. The normality of the data was verified using the test and Kolmogorov-Smirnov and Shapiro- Wilk. The variables studied with normal distribution (NFKB p65, M1, M2, KI67) were presented using means and standard deviations (SD). For the inferential analysis, One-way ANOVA was used followed by the Bonferroni post hoc comparison test. The data with non-normal distribution were then analysed with Kruskal- Wallis followed by Dunn's post hoc comparison test. The abnormal variables (degeneration, necrosis, infiltration and organization, collagen levels and cross-sectional area) were presented as medians and interquartile ranges (first and third). The level of significance was set at 5%.

Results

Cell Damage

Regarding the four indicators of cell damage, it was evident that the statistical differences between the groups follow in tissue degeneration, necrosis, and infiltration as expressed in table 1. The values in the degeneration process increased in TR1 and even more in TR3, training requirement, as well as for necrosis and infiltration. For the cellular organization the values were maintained.

Table1. *Representation of cell damage between different training levels.*

	Degeneration	Necrosis	Infiltration	Organization
SED	0 (0-1.0) * #	0 (0-0) * #	0 (0-0) * #	0 (0-0)
TR1	1.0 (1.0-2.0)	1 (0-1)	1.0 (0-1.0)	0 (0-0)
TR3	2.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0 (0-0)

Values are described in median 1st and 3rd quartile. * p <0.0001 vs. TR1; # p <0.0001 vs. TR3.

Collagen Levels

Eccentric training induced an increase in the levels of collagen in cardiac fibers specifically between the SED group with TR1 and SED with TR3, as shown in figure 1. There was an increase in collagen from the first week of training, increasing over time indicating a remodelling of the cardiomyocytes attributed by a process of adaptation to exercise.

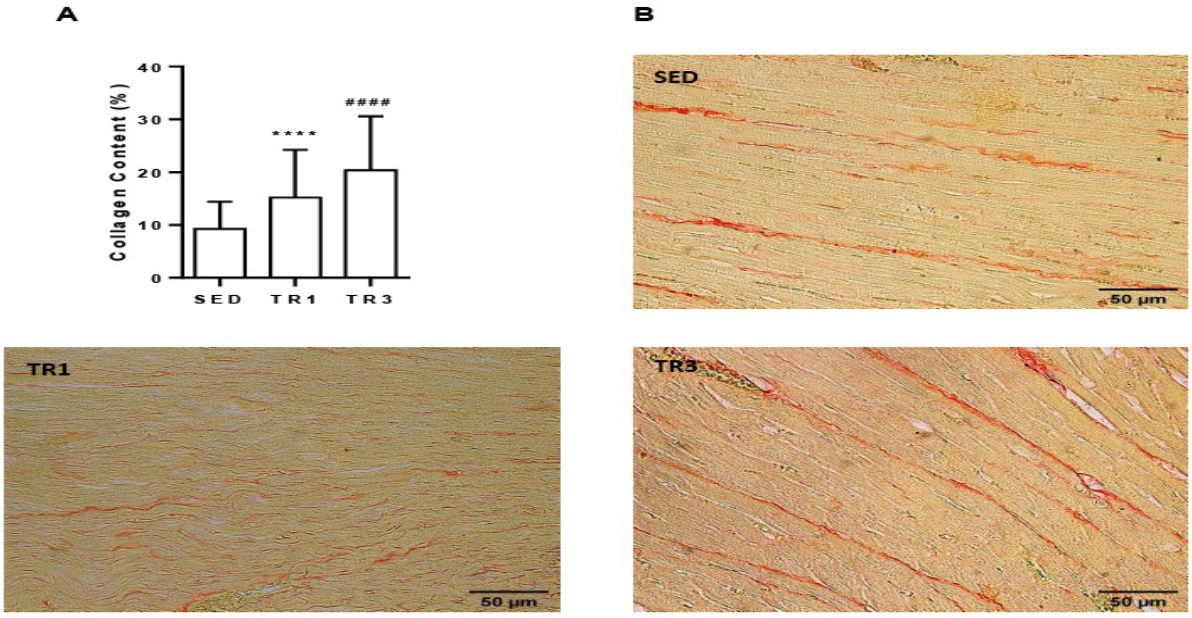

Fig1. *Characterization of the collagen content between the groups in the eccentric exercise represented in A. Light micrographs representative of the cardiac muscle of the sedentary group (SED), subgroup of eccentric exercises of the week (TR1) and subgroup of eccentric exercises of the week (TR3), stained with Picrosirius Red, are represented in B.**** p<0.0001 vs. SED; #### p<0.0001 vs. SED.*

Cross-Sectional Area

Eccentric training also induced a significant increase in the cross-sectional area between the SED and TR3 with a p <0.0001. Between the TR1 and TR3 groups, we found a significant relationship of p <0.0001, as shown in figure 2. Although in TR1 there is no significance between the SED, it is observed that the values represent an increase in TR3 meaning that the cells were overloaded by mechanical action undergoing an adaptation.

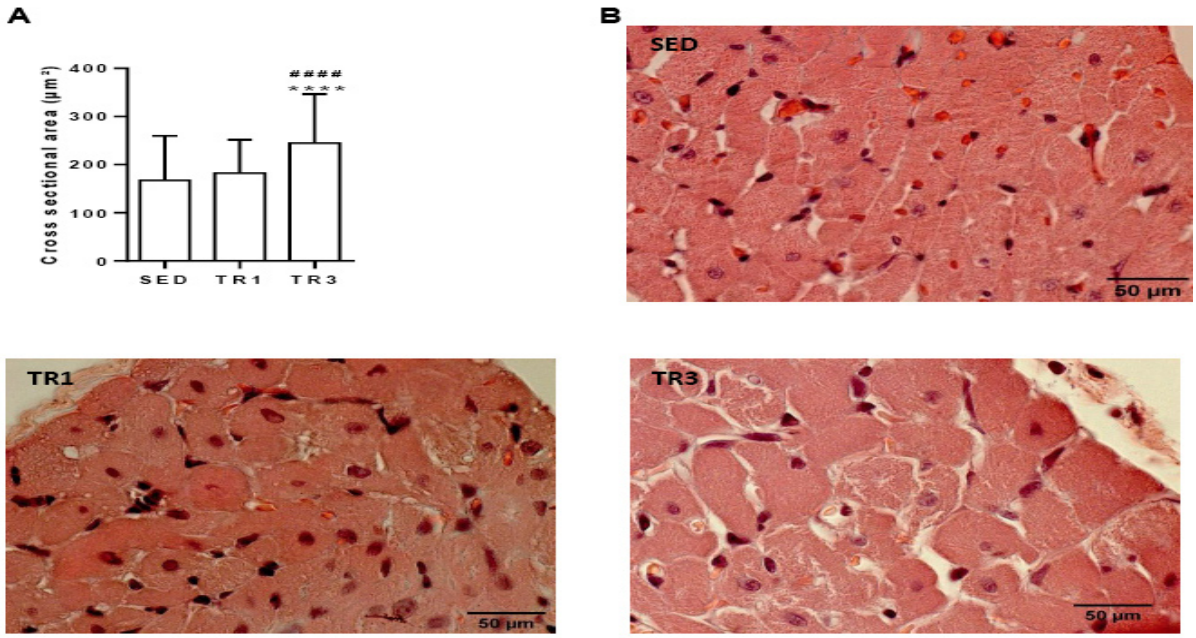

Fig2. *Characterization between groups in cross-sectional area in the eccentric exercise represented in A. Light micrographs representative of the cardiac muscle of the sedentary group (SED), subgroup of eccentric exercises of the week (TR1) and subgroup of eccentric exercises of the week (TR3), stained with Haematoxylin and Eosin, are represented in B.**** p<0.0001 vs. SED; #### p<0.0001 vs. TR1.*

Macrophage M1

In the case of the M1 macrophage, significant differences were found throughout the training period, established by figure 3. An increase in density is observed over time, meaning a picture of inflammation and interaction with adaptive immunity.

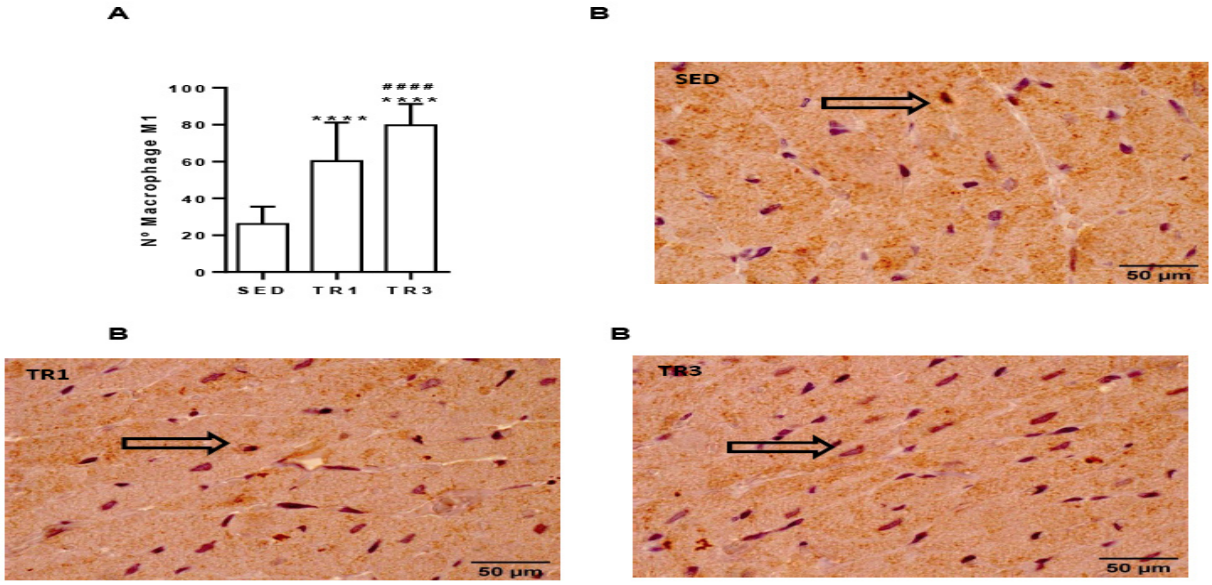

Fig3. *Characterization between the polarization groups of M1 macrophages in eccentric exercise represented in A. Light micrographs representative of the cardiac muscle of the sedentary group (EDS), eccentric exercise subgroup of the week (TR1) and eccentric exercise subgroup of the week (TR3), supported by M1 Macrophage Immunohistochemistry, are represented in B.**** p<0.0001 vs. SED; #### p<0.0001 vs. TR1.*

Macrophage M2

Regarding the marking of the M2 macrophage, in which they play an important role in the tissue repair process, there was a significance between the SED and TR1 with $p = 0.0096$, and illustrated in figure 4. It can be seen that there was a decrease in the repair process in the first week and that even with the increase in TR3 it was not shown to be significant in the process, which can be assumed of a harmful process to the cardiac tissue due to excessive exposure.

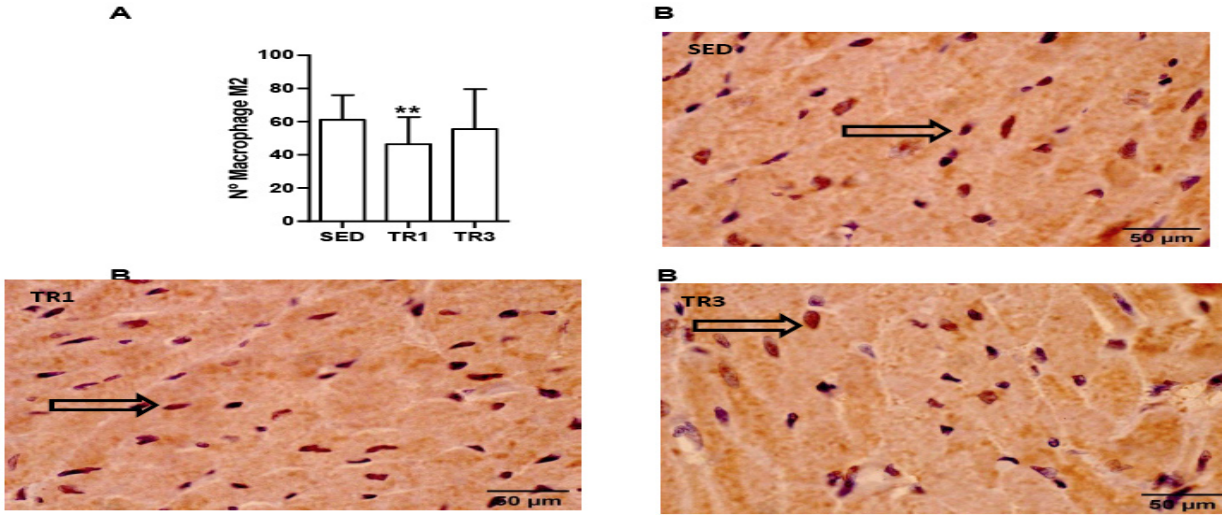

Fig4. *Characterization of the groups of macrophages polarization M2 in eccentric exercise represented in A. micrographs of representative light of the heart muscle group sedentary (SED), eccentric exercise subgroup of the week (TR1) and eccentric exercise subgroup of the week (TR3), supported by Immunohistochemistry Macrophage M2, are represented in B. ** p=0.0096 vs. SED.*

Macrophage NF- κB

For the marking of the NF- κB macrophage, related to the cellular response as stimuli of stress and inflammation, it was expressively identified that in the first week of activity such cellular response is already observed when compared to the sedentary one *(p<0.001)*, which this time was significantly related to the 3-week training *(p<0.001)*, as shown in figure 5. A decrease in the cellular response in TR3 to the stimuli was observed when compared with TR1.

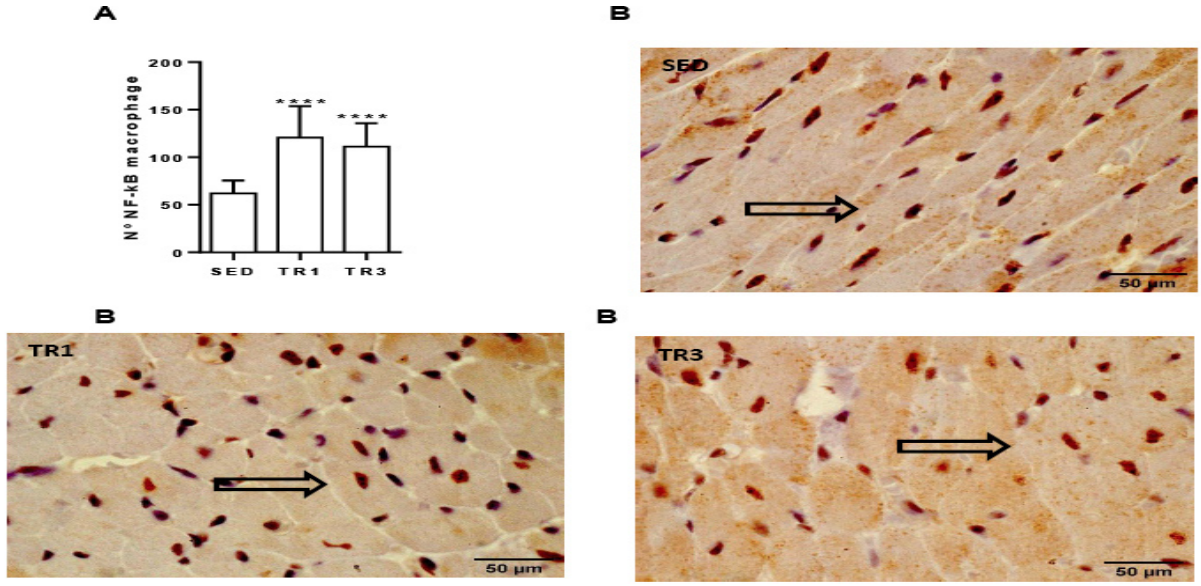

Fig5. *Characterization between groups of polarization NF- κB in eccentric exercise represented in A. micrographs of representative light of the cardiac muscle of sedentary group (SED), eccentric exercise subgroup of the week (TR1) and eccentric exercise subgroup of the week (TR3), supported by NF- κB Macrophage Immunohistochemistry, are represented in B. **** p<0.0001 vs. SED*

Macrophage Ki 67

For the above macrophage were found significant differences in the process of physical activity related to cell proliferation in an attempt to repair the damage as shown in figure 6. There was a decrease in the first week with a significant increase for the repair of tissue cardiomyocytes in TR3.

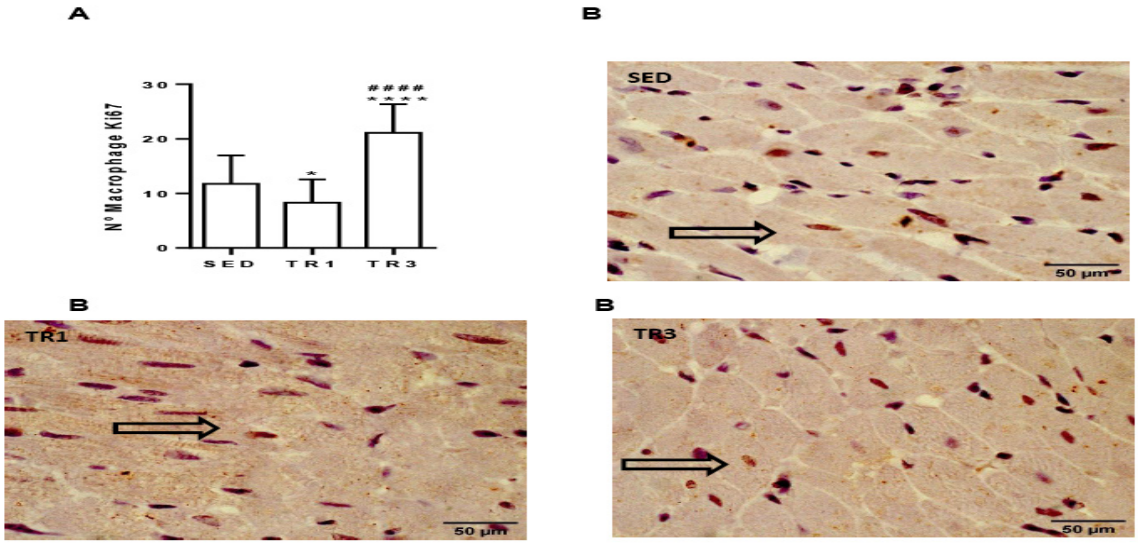

Fig6. *Characterization between the tissue repair groups by Ki-67n and the eccentric exercise represented in A. Light micrographs representative of the cardiac muscle of the sedentary group (SED), subgroup of eccentric exercises of the week (TR1) and subgroup of eccentric exercises of the week (TR3), supported by Macrophage Ki67 Immunohistochemistry , are represented in B.**** p<0.0001 vs. SED; #### p<0.0001 vs. TR1; * p=0,0211 vs. SED.*

Discussion

The results obtained demonstrated that the different levels of high intensity eccentric exercise caused damage to the cardiomyocytes, even with the evidence of tissue remodelling during the entire process of physical activity.

In the present study, the damage to the cardiomyocyte tissue may be related to the intensity of physical activity managed by the imposed protocol. In a similar study we studied the soleus and tibialis muscle, reported that the muscle damage shows different behaviours depending on the type of work each muscle conducts (29).

The muscle damage was induced by the requirement of eccentric exercise as it increased the exposure time of the activity. In the literature, we found studies that state that muscle contractions associated with greater mechanical tension are likely to cause greater damage to contractile proteins (5).

The entire process of inflammatory response was evidenced in the current study from the first week of activity, represented by TR1. Currently, the process and inflammatory response is generally accepted that if well regulated are essential for repair and muscle regeneration, although the inflammation has historically been seen as detrimental to the recovery of the exercise (30). The metabolic stress and the mechanical alterations contemplated to the muscular damage, stimulate several types of cells that comprise the skeletal muscle to start the process of the inflammatory responses (5).

Our data also showed a marked increase in the area of muscle collagen content along with an increase in the cross-sectional area in eccentric exercise, showing that there was an adaptation during the intense protocol at different levels of physical activity, as corroborated with another study (31).

The eccentric training induced an increase in the cross-sectional area in the cardiac fibres specifically between the SED group with TR1 and SED with TR3. We can also state that the eccentric training also induced a significant increase in the cross-sectional area between the SED and TR3. All this change projected by the level of activity related to the intensity associated with the repetitive exposure of the exercise to which the muscle undergoes generates stress that produces structural and ultra-structural changes that are affected by the different types of muscle contraction (32).

It is well established that the adaptations of the skeletal muscle, cellular stress and the resulting metabolic signals for mitochondrial biogenesis depend largely on the intensity of the exercise (30), as corroborated with our study.

It is well documented about the intensities of physical training in water protective factors in the myocardium (33) (34), high and medium intensity training in elderly rats (35), high intensity in the dynamic patterns of the macrophage phenotype in skeletal muscle through eccentric stimuli induced by exercise (36), the role of exercise in the damage plasticity (37)

After muscle injury induced by more severe exercise, recovery, that is, the entire recurrent inflammatory process will depend on the extent of the initial muscle damage, which is influenced by the intensity and duration of the exercise (38). In our study, we observed tissue repair denoted in reference to M2 immunohistochemistry between SED and TR1, which may suggest that there was a regenerative process in the first week of the applied eccentric exercise. After the following weeks, despite the increase in regeneration cells, no significant differences were found between SED and TR3, or even TR1 and TR3.

Conclusion

The eccentric exercise practiced during the first three weeks induced cellular responses to stress stimuli in the cardiac tissue, maintaining apoptosis and phagocytosis throughout the pro-inflammatory process through the interaction of adaptive immunity.

The tissue repair and healing process in the myocardium started in the first phase of the implementation of eccentric exercise and induced the proliferation of collagen and the adaptation of muscle fibers in the cross-sectional area.

The continuous process of high intensity eccentric exercise in the third week, on the other hand, did not show any significance for the repairing cells, which may characterize a tissue data due to the exercise requirement or the non-intermittence in physical activity.

Thus, despite the potential benefits from the metabolic point of view, public health efforts should also focus on maintaining levels of physical activity since our study showed that intense physical activity had harmful effects at the cardiac level.

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