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Exercise training plays cardioprotection through the oxidative stress reduction in obese rats submitted to myocardial infarction

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Increased oxidative stress may contribute to the pathogenesis of cardiovascular disease, and clinical and experimental studies have suggested that these diseases are associated with oxidative damage in either cardiac and aortic cells due to increased formation of free radicals and/or reduction of the antioxidant defenses [1]. Oxidative stress in obese individuals increases the susceptibility to oxidative damage. Several studies have shown a high level of ROS in obese individuals [2–4]. Although the role of antioxidant system remains uncertain concerning prevention or protection against the tissue damage induced by myocardial infarction, accumulating evidence demonstrates that the deficiency on antioxidant system renders the heart vulnerable to ischemia–reperfusion injury in animal models [5,6]. Exercise training induces cardioprotection against myocardial ischemia–reperfusion injury [7]; however, the role of antioxidant

response induced by exercise is unknown. Recently, we demonstrated that chronic exercise reduces ROS and increased the survival in lean rats submitted to experimental infarction [8]. However, the cardioprotective effects of exercise training (ET) and oxidative stress in obese rats have not been investigated. Thus, we sought to determine the effects of ET on oxidative stress in myocardial and aorta of obese rats submitted to experimental infarction.

Male *Wistar* rats were fed on standard chow or high fat-diet for two months, as previously described [9]; thereafter, obese rats were submitted to exercise training (nine-channel motor-drive treadmill at 1 km/h for 50 min/d, 5 d/wk) for two months (Fig. 1A).

As expected, high-fat diet increased the total body weight and epididymal fat weight in rats (Fig. 1B and C). Exercise training did not change total body weight, though it reduced epididymal fat content (Fig. 1B and C). At the end of the exercise protocol, high levels of superoxide anion, TBARS and carbonyl were found in myocardial and aorta of obese animals, compared with the lean group. Conversely, exercise reduced these oxidative stress markers in myocardial tissue and aorta in obese animals, when compared with the obese group at rest (Fig. 1D–I). This data are in accordance with previous studies performed in lean animals [8,10].

Next, we investigated antioxidant enzyme activity, such as, SOD, GPx and catalase. These assays were performed as previously described [8]. SOD and GPx activities were reduced in myocardial and aorta tissues of the obese group, when compared with the lean animals. However, the chronic exercise increased the activity of these enzymes in both tissues of obese animals, when compared with the obese group at rest (Fig. 1J–M). These data are important, for a number of reasons. First, a reduction in CuZn-SOD and GPx activity and protein levels was observed in human erythrocyte from obese subjects, compared to normal weight individuals [4,11]. Second, high level of

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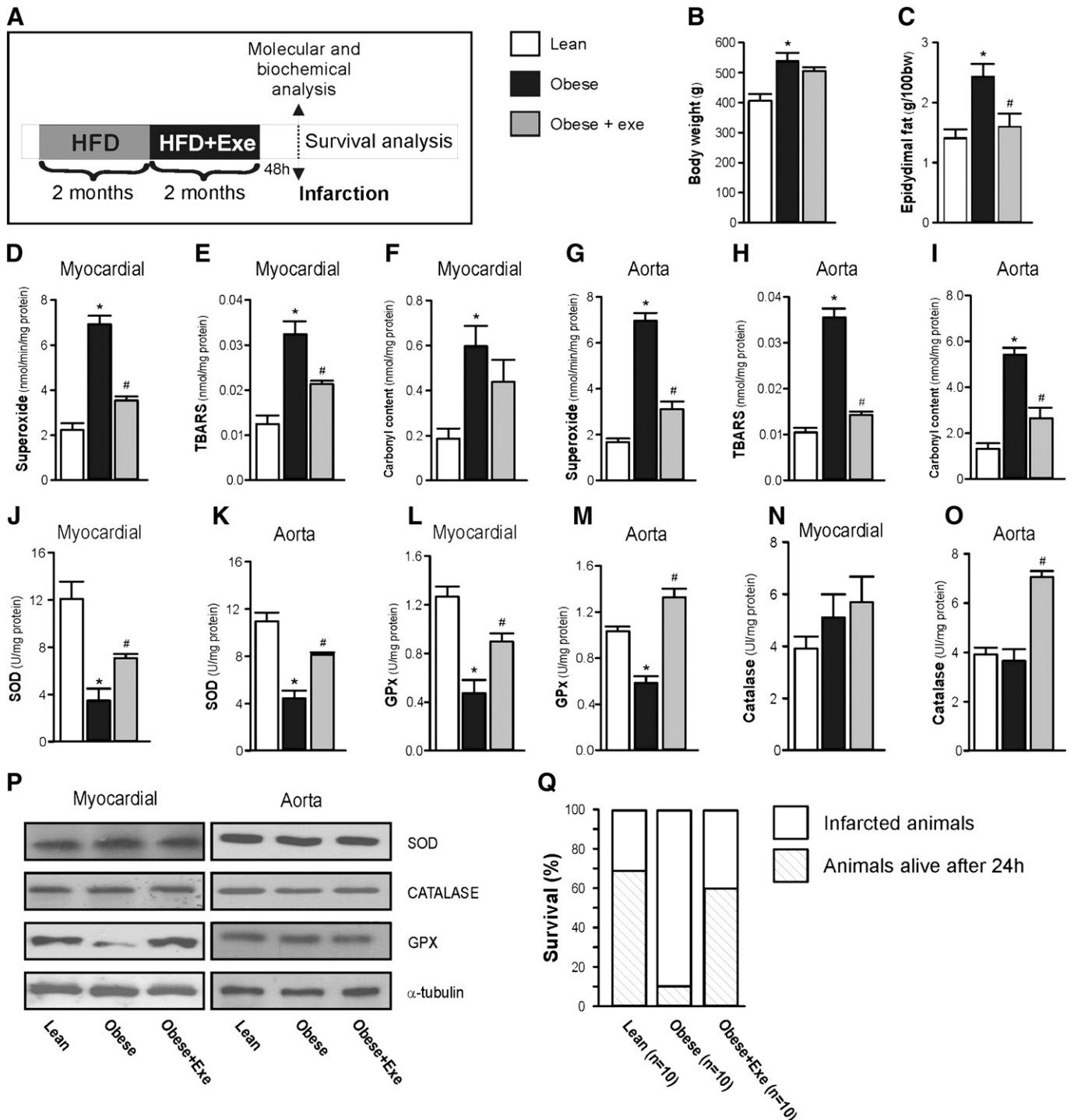


Fig. 1. Effects of exercise on antioxidant enzymes activity in myocardial and aorta of obese rats and effects of exercise on survival in rats submitted to experimental infarction. A – Schematic representation of the experimental procedures. B – Total body weight. C – Epididymal fat. D–O – Superoxide anion (SOD), thiobarbituric acid-reactive substances (TBARS), carbonyl and SOD, catalase (CAT) and glutathione peroxidase (GPx) activity and protein levels in both the myocardial and aorta tissues of studied groups. P – Western blot was performed to evaluate the SOD, catalase and GPx expression in myocardial and aorta of rats. Comparisons among groups were made using parametric one-way ANOVA; where F ratios were significant, and further comparisons were made using the Bonferroni test. Bars represent mean \pm SEM of rats ($n = 10$). * $p < 0.05$, obese vs. lean group; # $p < 0.05$, obese trained vs. obese group. Q – Survival analysis was performed 24 h after experimental infarction ($n = 10$ animals per group). Animal survival was compared using chi-square test, because we had a single time point observation and the level of significance was set at $p < 0.001$. The software used for analysis of the data was the Statistical Package for the Social Sciences (SPSS) version 16.0 for Windows.

superoxide anion was observed in the endothelium of the coronary arteries of obese animals, and it was related to endothelial dysfunction [12]. Third, a high production of superoxide ventricular is coupled with a decrease in cardiac function [13]. Finally, $Sod^{-/-}$ mouse hearts were more susceptible to ischemic reperfusion injury [6]. Thus, the cardioprotective mechanism of exercise in obese on endothelial and

myocardial dysfunction could be associated with reduced oxidative stress and increased capacity of antioxidant enzymes [14].

On the other hand, catalase activity was similar in myocardial tissues of both groups (Fig. 1N). We observed that catalase activity was increased in aorta of obese exercised animals, when compared with the obese group at rest (Fig. 1O). Our results regarding SOD and

catalase activity in myocardial of exercised animals are in accordance with the study published by Hong and Johnson [15]. The authors also observed an increase in cardiac activity of SOD in exercised animals, but activity of CAT remained unchanged [15]. It is important to note that, although studies indicate that antioxidants improve heart muscle function, its adaptation to the antioxidant system depends on tissue analyzed and type, intensity and duration of exercise [16].

Western blotting analysis showed that SOD and Catalase protein levels were similar among the groups in both tissues (Fig. 1P). In myocardial tissue, GPx protein expression was reduced by about 70% in obese animals, when compared to the lean group; however, exercise restored the GPx expression in myocardial tissue of obese animals (Fig. 1P). GPx expression was similar in aortas of both groups (Fig. 1P). These findings showed that the effects of exercise on the myocardium and aorta of obese rats appear to occur at the level of enzyme activity rather than the protein levels.

Since the deficiency of antioxidant response is associated with vulnerability of the myocardial infarction and ischemia-reperfusion injury [6,8], we sought to determine whether antioxidant effects of exercise could increase the survival during experimental infarction in obese animals. Thus, 48 h after the last session of exercise, lean, obese and exercised obese rats were submitted to infarction by using subcutaneous injection of isoproterenol hydrochloride (60 mg/kg) ($n = 10$ animals per group). We observed that obese group presented high levels of mortality ($p < 0.001$), when compared with lean rats. Only one obese animal survived after experimental infarction. Interestingly, exercise increased the rate of survival of infarcted animals, when compared to the obese group at rest (Fig. 1Q).

The increase in survival rate in exercised animals after the experimental infarction occurred, at least in part, due to the modulation of the antioxidant system, though we cannot exclude the possibility that other factors, such as anti-inflammatory action, structural and functional myocardial and vascular adaptation could be associated with this phenomenon.

Collectively, exercise training resulted in low formation of superoxide anion and minor damage to lipids and proteins, probably due to increased activity of SOD and GPx. Furthermore, the reduction in percentage of death in obese rats may be related to lower levels of oxidative stress, as a cardioprotective mechanism.

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A new graphical method for the estimation of the corrected QT interval

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The QT interval provides an indirect estimation of the duration of the electrical systole. Abnormal short and long QT intervals are associated with increased risk of syncope and sudden death [1]. Also, an increasing number of noncardiac drugs have the potential for serious proarrhythmic effects related to QT prolongation. Thus, health care professionals in all fields of medicine, ranging from pediatrics to neurology, can encounter patients with abnormal QT duration.

Because of its inverse relationship to heart rate, the QT interval should be corrected for heart rate. Many correction formulas have