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The Therapeutic Effect of Endurance Training on Adriamycin-induced Cardiac Stress in Rats

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Abstract

Purpose: In recent years, by understanding the free radical mechanism of Adriamycin(ADR)-induced cardiac stress, it has become possible to develop effective strategies to prevent or modify their expected damages. Several strategies for detecting and preventing cardiac stress have been developed, including physical activity or limiting their accumulation. The purpose of this study was to determine the preventive effects of endurance training on various doses of adriamycin-induced cardiac stress in rats.

Material and Methods: Forty-eight male rats were randomly assigned to non-training (NT) and training (T) groups with three subgroups; including $ADR_{10mg.kg}^{-1}$, $ADR_{20mg.kg}^{-1}$ and saline treatment. Training program included treadmill running for 25 to 54 min/day, 15 to 20 m/min, 5 days/week, for 6 weeks. After the last exercise session of the training groups, a new randomization of all groups into subgroups was performed as follows: non-training+saline(NT+saline); non-training+$ADR_{10mg.kg}^{-1}$(NT+ADR_{10}); nontraining+$ADR_{20mg.kg}^{-1}$(NT+ADR_{20}); training+saline(T+saline); training+ADR_{10}(T+ADR_{10}) and training+ADR_{20}(T+ADR_{20}) and afterwards, injections were performed. Rats in all the groups were anesthetized with ketamine and xylazine after 10 to 12 hours of overnight fast.

Results: $20_{mg.kg^{-1}}$ of ADR administration, caused an imbalance in markers related to cardioprotection(HSP_{70}, SOD) and cardiac stress (MDA, CPK-MB, CK), as compared to NT+saline group. Preventive effect of endurance exercise in the presence of ADR with$10_{\text{ and }}20_{mg.kg^{-1}}$ caused a significant increase in HSP_{70}, SOD and an insignificant and significant decrease in MDA, an insignificant decrease and a significant increase in CPK-MB and an insignificant decrease in total CK in comparison with NT+ADR_{10} and NT+ADR_{20} respectively. However, there was no significant difference between T+$ADR_{10mg.kg^{-1}}$ and T+$ADR_{20mg.kg^{-1}}$ in HSP_{70}, MDA and total CK but there were significant differences in SOD and CPK-MB. ADR-induced cardiac stress is related to oxidative stress.

Discussion and Conclusions: Our study suggests that pre-treatment with endurance exercise may be considered as a potentially useful strategy for improving myocardial tolerance against ADR-induced oxidative damage. The biochemical mechanisms through which pre-treatment with endurance exercise training exerts its potential antioxidant properties, protects cardiac muscle tissue against the toxicity ADR-induced.

Keywords: Endurance training, Adriamycin, Cardiotoxicity, HSP_{70}

Introduction

Adriamycin (ADR) is a powerful and highly efficacious drug and shows a broad range of antitumor activity in many kinds of cancers [1]. Despite extensive clinical utilization, the action mechanisms of ADR remain under intense debate. A growing body of evidence supports the view that this drug can be a double-edge sword. However, the clinical use of ADR is often limited because of its undesirable serious cardiac stress side effects on cardiac tissues [2, 3, 4, 5, 6, 7]. Several researchers have reported that an organism is generally protected from damage caused by free radicals by means of its antioxidant defence system [8]. In recent years, by understanding the free radical mechanism of ADR-induced cardiac stress, it has become possible to develop effective strategies to prevent or modify the expected damage. To date, a number of pharmaceutical agents have been tested, to assess their potentiality to reduce the risk of

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adriamycin-related cardiac stress [6, 9, 10, 11, 12]. ADR is significantly toxic to most tissues and organs, but its cardiac side effects and its hepatotoxicity are the limiting factors in the cancer therapy with this agent [13]. Several strategies for detecting and preventing cardiotoxicity have been developed, some of which are more effective than others including limiting its cumulative dose, altering anthracycline administration, using anthracycline analogues, adding cardioprotectants to the regimen and employing nutritional supplements [14]. It seems probable that regular endurance exercise training could constitute an excellent tool either to prevent and/or to treat several diseases. Also, most recent studies have focused on the healing effects of endurance exercise on ADR-induced cardiac stress [15, 16, 17]. Prior endurance exercise as a nonpharmacological strategy may possibly promote defensive effect of ADR against cardiac stress [17, 18, 19]. However the mechanism(s) by which exercise training protects cardiomyocytes against these myocardial insults remains unknown [16]. Heat shock proteins (HSPs) possess a chaperone-like activity and have a key role in maintaining normal cellular functions and restoration after an insult [20, 21]. Simoncikova et al reported that chronic administration of ADR to rats induces upregulation of HSP_{60} and down-regulation of HSP_{70} in the cardiac tissue [22] and researchers have stated that moderate intensity exercise training is effective in preventing HSP_{70} increase [23]. The preventive role of regular endurance exercise as an antioxidant factor on HSP_{70} in the heart has not been sufficiently studied while most recent studies have focused on the curative effect of endurance exercise on ADR-induced cardiac stress [15, 16, 17, 24].

We are the first to investigate the cardioprotective effects of prior (pretreatment) treadmill running endurance exercise on HSP_{70} and adriamycin-induced cardiac stress with various dosages. The hypothesis proposed was that if ADR-induced cardiac stress is related to free radical formation and oxidative stress, an enhancement in antioxidant/oxidation ratio after regular endurance exercise may protect the heart against ADR-induced toxicity . Therefore, the purpose of this study was to determine pre-treatment effects of endurance exercise on heat shock proteins (HSP_{70kda}) - as a cardioprotection protein-, superoxide dismutase (SOD)- as an enzymatic antioxidant, malondialdehyde (MDA), cardiac isoenzyme of creatine phosphokinase (CPK-MB), and total creatine kinase (total CK) - as biomarkers related to cellular oxidative damage, after a multi-dose administration of ADR.

Material and Methods

Experimental Design and Laboratory Environment;

The experimental protocol of the current study was approved by the department of physiology, university of Mazandaran and was performed according to guiding procedures in the Care and Use of Animals, prepared by the Council of the American Physiological Society. The experiments were carried out with forty-eight Wistar male rats (10 weeks old, initial weight 251 ± 32 g), which were obtained from Pasture institute of Iran. Rats were housed in standard cages of polycarbonate (20 × 15 × 15 cm), made at Pasture institute of Iran, in a large air-conditioned room with a controlled temperature of 22 ± 2°C, light- dark cycles of 12 : 12 hours and humidity of 50 ± 5%. The pollutant standard index (PSI) was in the acceptable range as determined by the Iranian meteorological organization. Rats were fed with a standard rat chow provided by Pars Institute for animals and poultry with a daily regimen of 10 g per 100 g of body weight for each rat. Water was available ad libitum.

Familiarization and Exercise Training Protocols

Animals were randomly divided into two groups: training (T) and non-training (NT). Rats in both groups were adapted to the treadmill running for one week. The familiarization protocol was designed as once a day, 10 $min.session^{-1}$, at 10 $m.min^{-1}$,with a slope of 0 degree. Because rats are more active in darkness [25], the front ends of the treadmill lines were covered with a thick, dark paper.

Exercise Training protocol and Subjects' Classification

Subjects in the training group were assigned to perform a regular endurance running on treadmill. The training protocol consisted of a 5-minute warm-up run followed by a 25 to 54 min/session, 15 to 17 m/min, with zero slope, 5 days/week, for 6 weeks. All groups rested 24 hours after the last exercise session and then were randomly assigned to the following subgroups: non-training+ saline (NT+saline); nontraining+ $ADR_{10mg.kg}^{-1}$($NT+ADR_{10}$);non-training+ $ADR_{20mg.kg}^{-1}$ ($NT+ADR_{20}$); training+ saline (T+ Saline); training+ ADR_{10} ($T+ADR_{10}$) and training+ ADR_{20} ($T+ADR_{20}$).

There were eight rats in each group.

ADR treatment

ADR was obtained from EBEWE Pharma Ges.m.b.H.Nfg.KG (A-4866 unterach, Austria) as a vial of ph. Eur. In order to reduce the drug concentration to 10 and $20_{mg.kg^{-1}}$, it was dissolved in 0.9% saline before administration. The $20_{mg.\ kg^{-1}}$ dose of ADR is the human clinical dose that was pharmacologically scaled to be used in rats [26]. Saline was used as the vehicle and the placebo treatment and was used to make saline solution (0.9% NaCl ip).

Heart Tissue collection and preparation

Rats in all groups were anesthetized with ketamine (30–50 mg/kg of body weight, ip) and xylazine (3–5 mg/kg of body weight, ip) after 10 to 12 hours of overnight fasting and were placed in the supine position. The abdominal cavity was opened to expose the left ventricle and a 2-ml blood sample was collected in a tube. Then hearts were quickly excised, rinsed, carefully dried, weighed and placed into Petri dishes containing cold isolation medium (0.1 mol/L K2HPO4, 0.15 mol/L NaCl, pH 7.4) to remove the blood. They were then frozen immediately in liquid nitrogen and were stored at -80ºC. Heart samples were homogenized in a homogenization buffer (0.05 M Tris, 0.03 M L-serine, and 0.06 M boric acid, pH 7.6; 100 mg of tissue/ml of buffer) [27]. 5 ml/g of tissue with a protease inhibitor cocktail for mammalian cell and tissue extracts (Sigma Aldrich, St. Louis, U.S.A) 100 ul/1 ml, and 10 mMtris base (Sigma-Aldrich, St. Louis, U.S.A), pH 7.4 was centrifuged at 1500 g at 4 ºC for 15 min. Heart supernatant was diluted 1:30. Plasma was diluted 1:10, and was homogenized in double distilled water.

Homogenates were centrifuged (for 2 min at 2,000 g, 4°C) to eliminate cellular debris, and the resulting supernatant was stored in liquid nitrogen (-80°C) for later determination of HSP_{70}, SOD, MDA (cardiac ventricle). blood sample was first centrifuged by a refrigerated centrifuge at 3,000 rpm for 15 minutes within 30 minutes of collection, then the serum was separated and stored at -80 C before biochemical estimations of total CK and CPK-MB (Figure 1 shows the process of doing research protocol).

Biochemical analysis

Heat shock protein (HSP_{70}) in the heart was measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kits (Cusabio biotech co., LTD). In summary, 100µl of standard, Blank, or Sample was added per well. The liquid was removed from each well and 100µl of Biotin-antibody working solution was added to each well., each well was aspirated and washed three times. then 100µl of HRP-avidin working solution was added to each well and the aspiration and washing was repeated five times as the fourth step. Moreover, 90 µl of TMB Substrate was added to each well.50 µl of stop solution was also added to each well when the first four wells containing the highest concentration of standards developed obvious blue color. Finally, the optical density of each well was determined within 30 minutes; a microplate reader set to 450nm was used. Afterwards, the levels of SOD activity and MDA content of the supernatants were evaluated with superoxide dismutase assay kit (Cayman chemical campany) applying the method described by Chularojmontri et al (2005) [28] and thiobarbituric acid reactive substances (TBARS) were evaluated using Chularojmontri et al method [28]. Also, total CK and CPK-MB of the serum were measured using a CK-NAC, DGKC/IFCC method using a creatine kinase kit(darman kave-Iran) and a photometric method using CPK-MB kit(pars azmoon-Iran) Respectively.

Statistical analysis

All data have are expressed as mean±SD. Statistical analysis was performed using a commercial software package (SPSS version 16.0 for Windows). Data regarding cardioprotective and cardotoxicity biomarkers were normally distributed after log-transformation. A one-way analysis of variance (Statistics software, StatSoft, Inc., Tulsa, OK) was used to detect statistical differences between groups. A post-hoc test (Tukey test) was performed to determine differences in the various biomarkers between groups. Differences were considered statistically significant at $p < 0.05$.

Results

Table 1 shows changes in HSP_{70}, SOD, MDA, CPK-MB and total CK levels following adriamycin treatment in the study groups. Rats treated with Adriamycin (10 and 20 $_{mg.kg\text{-}1}$) in NT group, showed

an insignificant and a significant increase in HSP_{70} (23/7% and 30/4%, respectively), a significant decrease in SOD (9/4% and 22/5%,), an insignificant and a significant increase in MDA (51% and 136/1%, respectively), a significant increase in CPK-MB (472/7% and 479/6%, respectively) and a significant increase in total CK (509/4% and 653/6%), as compared to NT+saline group. Although, there was no significant difference between $ADR10_{mg.kg-1}$ and $ADR20_{mg.kg-1}$ treatments in HSP_{70}, CPK-MB and total CK levels, there was a significant difference between $ADR10_{mg.kg-1}$ and $ADR20_{mg.kg-1}$ treatments in SOD and MDA levels ($P < 0.05$). six weeks of regular endurance training led to a significant increase of heart HSP_{70}, SOD and total CK levels (97/5% , 36% and 562/3%, respectively), an insignificant increase in CPK-MB(314/7%) and an insignificant decrease in MDA, as compared to NT+saline group ($P < 0.05$) (Table 1). However, after six weeks of aerobic training and ADR treatment with $10_{mg.kg-1}$, a significant increase in HSP_{70} and SOD (56/1%and 34/4%, respectively), an insignificant decrease in MDA and CPK-MB (42/3% and 0/8%, respectively), and an insignificant increase in total CK (1/3%) were detected as compared to $NT+ADR_{10}$ group ($P < 0.05$). In contrast, six weeks of aerobic training and ADR treatment with $20_{mg.kg-1}$ resulted in a significant increase in HSP_{70} , SOD and CPK-MB (48/7%, 40/2% and 106/4%, respectively), a significant decrease in MDA (90/9%), and an insignificant decrease in total CK (53/5%) as compared to $NT+ADR_{20}$ group ($P < 0.05$). Changes between heart tissue HSP_{70}, SOD, MDA, CPK-MB and total CK levels, are shows in Figure 2, 3, 4, 5 and 6, respectively. After six weeks of aerobic training and Adriamycin treatment, (10 or $20_{mg.kg-1}$,) an insignificant decrease and an insignificant increase in HSP_{70} (2/2% and 2/7%, respectively), a significant decrease in SOD (10/8% and 18/9%, respectively), an insignificant and a significant increase in MDA (79/4% and 109/1%, respectively), an insignificant and a significant increase in CPK-MB (36/9% and 190/1%, respectively) and an insignificant decrease in total CK (7/2% and 34/9%, respectively) were detected, as compared to T+saline group ($P < 0.05$). However, there were no significant differences between $ADR10_{mg.kg-1}$ and $ADR20_{mg.kg-1}$ treatments in HSP_{70}, MDA and total CK levels while, there was a significant difference between $ADR10_{mg.kg-1}$ and $ADR20_{mg.kg-1}$ treatments in SOD and CPK-MB levels.

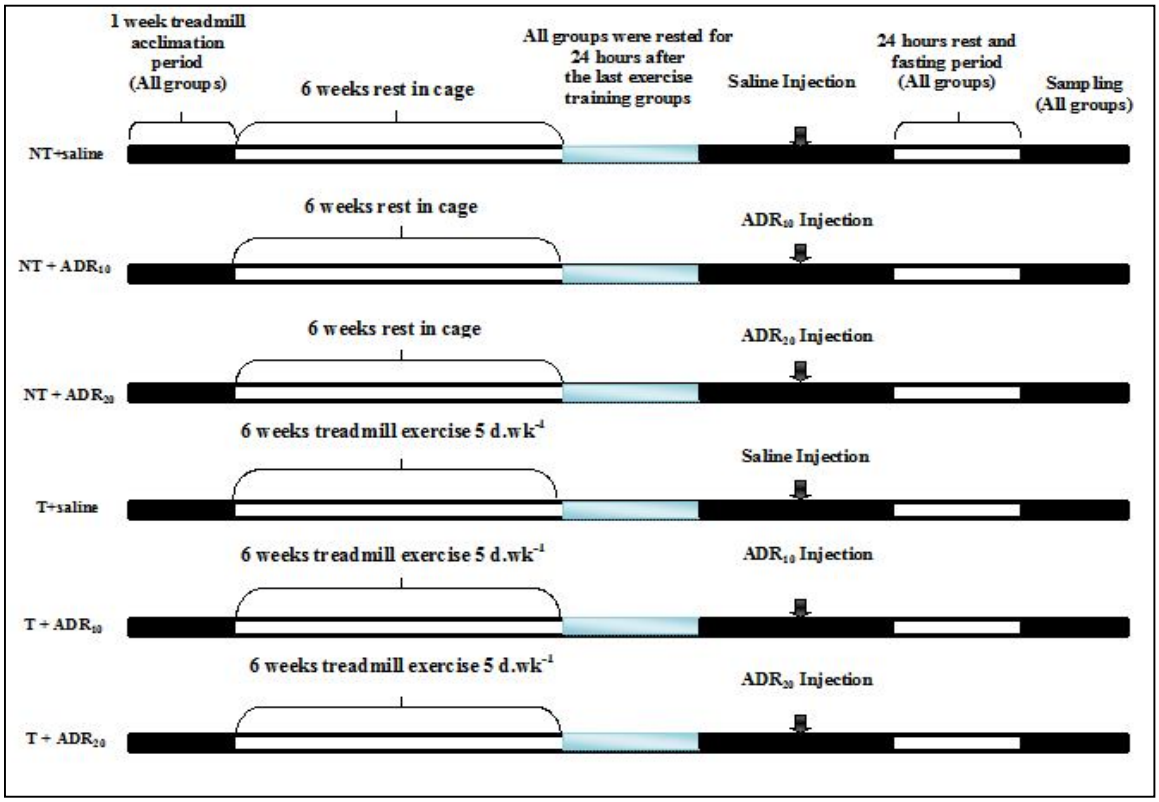

Figure 1: Diagram of the research protocol

Table 1: Levels of markers related to cardiac stress and damage in the study groups

Biomarkers	Groups					
	NT+saline	**NT+ADR$_{10}$**	**NT+ADR$_{20}$**	**T+saline**	**T+ADR$_{10}$**	**T+ADR$_{20}$**
HSP$_{70}$(ng/mg protein)	16/46±5/94	20/35±1/68	21/4±2/44	32/46±2/55	31/76±2/41	33/31±2/79
SOD(u/mg protein)	92/33±2/90	84/32±4/42	75/31±5/99	125/6±2/59	113/3±2/99	105/6±4/06
MDA(nmol/g protein)	29/63±1/89	44/72±3/67	69/91±22/11	17/53±7/07	31/41±6/96	36/65±6/73
CPK-MB(U/L)	8/85±1/2	50/47±1/93	51/34±2/15	36/52±2/85	50/06±5	105/9±9/36
Total CK(U/L)	115/7±69/3	705/1±387/2	872±457/3	766/3±408/3	714/8±483/9	567/8±456/5

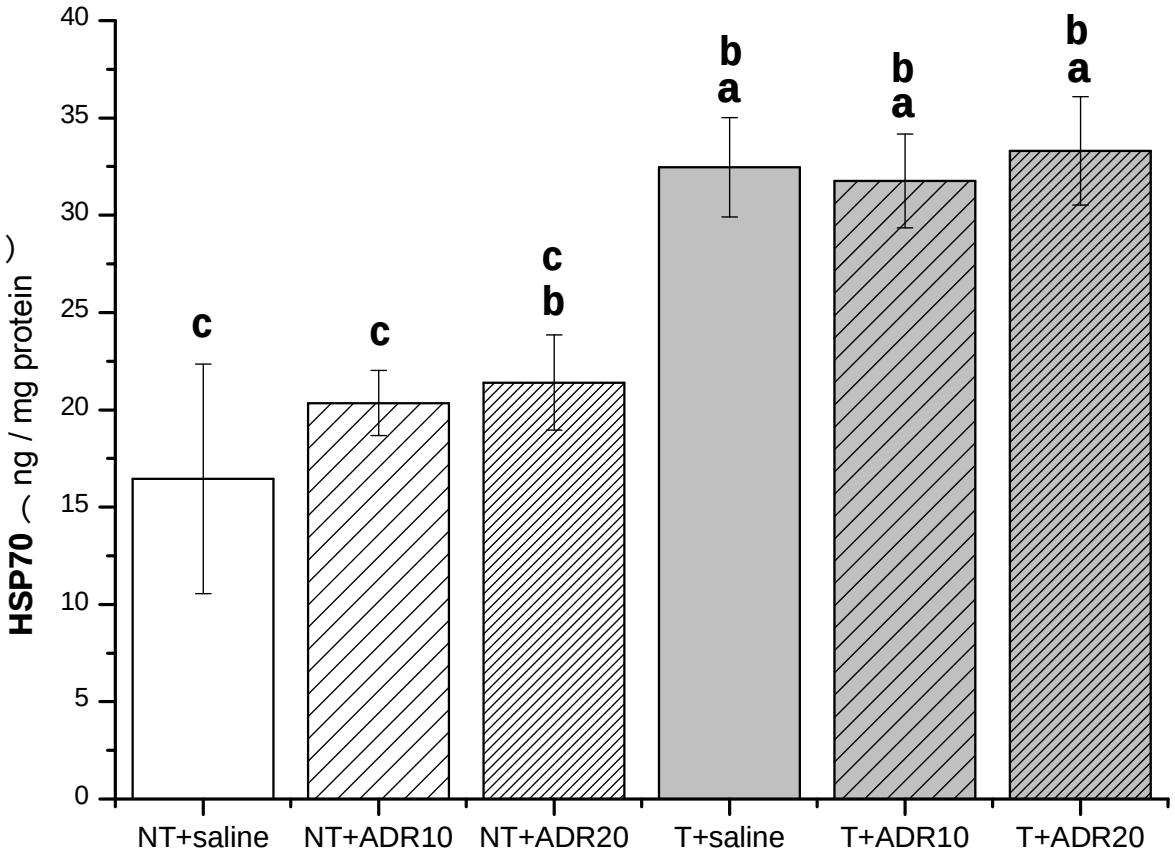

Figure2: Heat shock protein (HSP70) levels after six weeks of aerobic training and ADR treatment. Abbreviations; NT+saline (nontraining+Saline), NT+ADR10(nontraining + Adriamycin 10 mg.kg-1), NT+ADR20 (nontraining + Adriamycin 20 mg.kg-1), T+saline (6 weeks training+saline), T +ADR10 (6 weeks training + Adriamycin 10 mg.kg-1), T +ADR20 (6 weeks training + Adriamycin 20 mg.kg-1).Data are presented as mean±SD for 8 Rats. a: significantly different from similar nontraining group ($P<0.05$), b: significantly different from NT+saline group ($P<0.05$), c: significantly different from the T+saline group ($P<0.05$), d: significantly different from 10 mg.kg-1 dose in the same group ($P<0.05$).

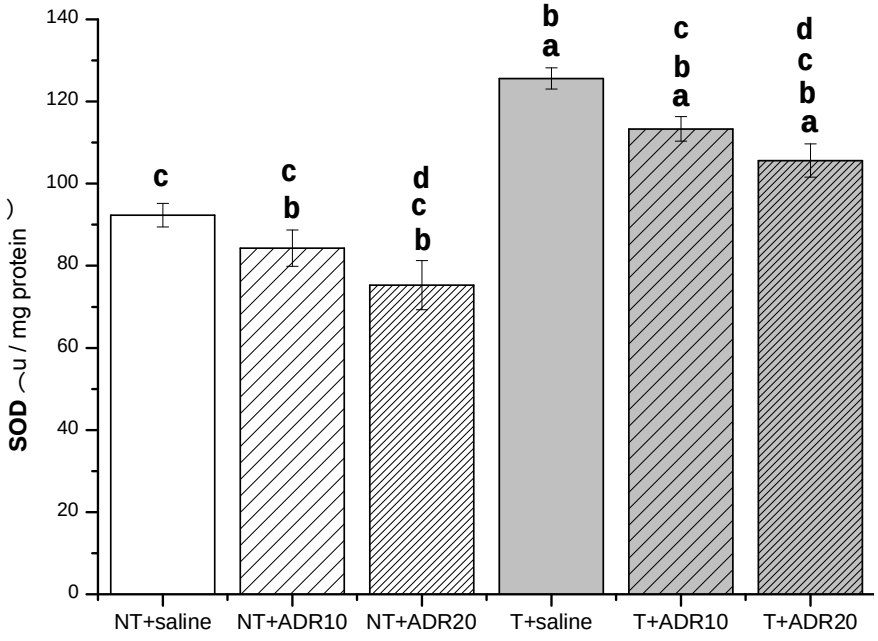

Figure 3: Superoxide dismutase (SOD) levels after six weeks of aerobic training and ADR treatment. Abbreviations; NT+saline (nontraining+Saline), NT+ADR10 (nontraining + Adriamycin 10 mg.kg-1), NT+ADR20 (nontraining + Adriamycin 20 mg.kg-1), T+saline (6 weeks training+saline), T +ADR10 (6 weeks training + Adriamycin 10 mg.kg-1), T +ADR20 (6 weeks training + Adriamycin 20 mg.kg-1).Data are presented as mean±SD for 8 Rats. a: significantly different from similar nontraining group (P<0.05), b: significantly different from the NT+saline group (P<0.05), c: significantly different from the T+saline group (P<0.05), d: significantly different from 10 mg.kg- 1 dose in the same group (P<0.05).

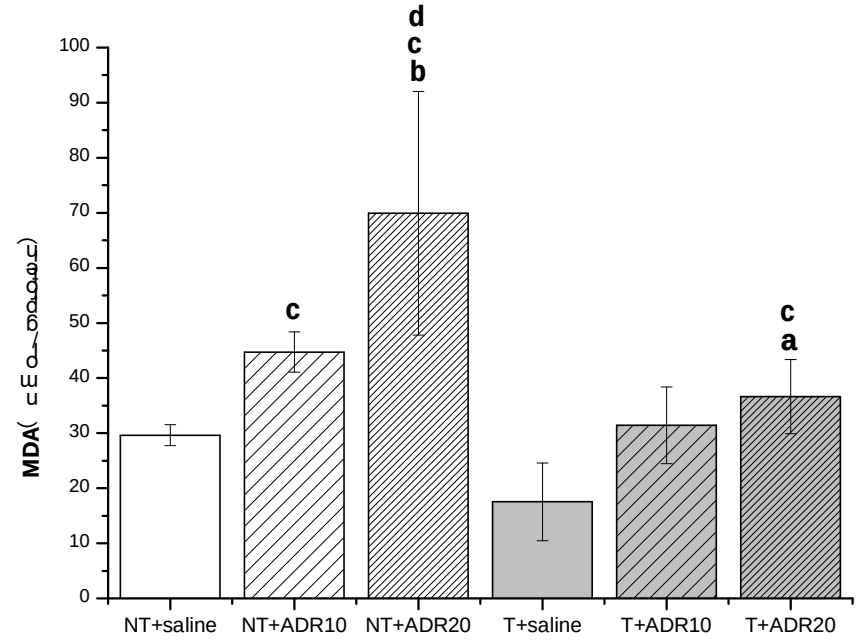

Figure 4: malondialdehyde (MDA) levels after six weeks of aerobic training and ADR treatment. Abbreviations; NT+saline (nontraining+Saline), NT+ADR10(nontraining + Adriamycin 10 mg.kg-1), NT+ADR20 (nontraining + Adriamycin 20 mg.kg-1), T+saline (6 weeks training+saline), T +ADR10 (6 weeks training + Adriamycin 10 mg.kg-1), T +ADR20 (6 weeks training + Adriamycin 20 mg.kg-1).Data are presented as mean±SD for 8 Rats. a: significantly different from similar nontraining group (P<0.05), b: significantly different from the NT+saline group (P<0.05), c: significantly different from the T+saline group (P<0.05), d: significantly different from 10 mg.kg-1 dose in the same group (P<0.05).

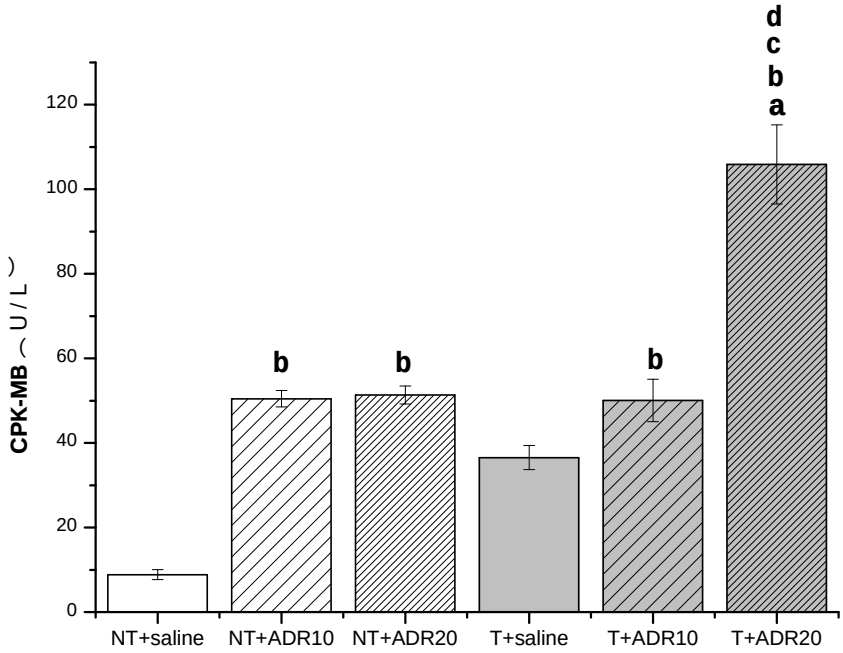

Figure 5: cardiac isoenzyme of creatine phosphokinase (CPK-MB) levels after six weeks of aerobic training and ADR treatment. Abbreviations; NT+saline (nontraining+Saline), NT+ADR10(nontraining + Adriamycin 10 mg.kg-1), NT+ADR20 (nontraining + Adriamycin 20 mg.kg-1), T+saline (6 weeks training+saline), T +ADR10 (6 weeks training + Adriamycin 10 mg.kg-1), T +ADR20 (6 weeks training + Adriamycin 20 mg.kg-1).Data are presented as mean±SD for 8 Rats. a: significantly different from similar nontraining group (P<0.05), b: significantly different from the NT+saline group (P<0.05), c: significantly different from the T+saline group (P<0.05), d: significantly different from 10 mg.kg-1 dose in the same group (P<0.05).

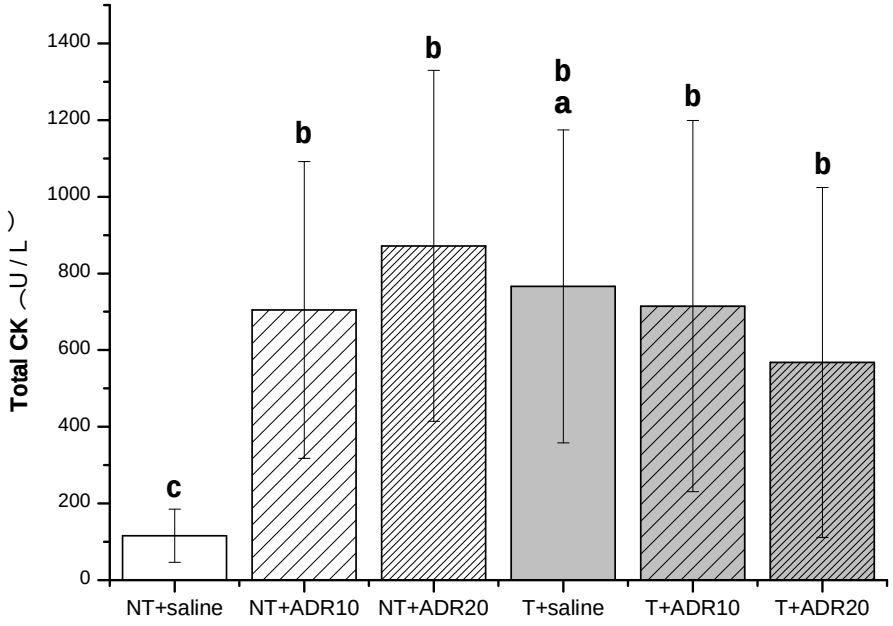

Figure 6: total creatine kinase (total CK) levels after six weeks of aerobic training and ADR treatment. Abbreviations; NT+saline (nontraining+Saline), NT+ADR10(nontraining + Adriamycin 10 mg.kg-1), NT+ADR20 (nontraining + Adriamycin 20 mg.kg-1), T+saline (6 weeks training+saline), T +ADR10 (6 weeks training + Adriamycin 10 mg.kg-1), T +ADR20 (6 weeks training + Adriamycin 20 mg.kg-1).Data are presented as mean±SD for 8 Rats. a: significantly different from similar nontraining group (P<0.05), b: significantly different from the NT+saline group (P<0.05), c: significantly different from the T+saline group (P<0.05), d: significantly different from 10 mg.kg-1 dose in the same group (P<0.05).

Discussion

There are several reports stating that the clinical application of ADR is marred by an increased risk of myocardial injury, which is mainly caused by reactive oxygen species from ADR disposition [16, 29]. Although, previous studies have focused on the role physical activity as a nonpharmacological strategy in treating various cancers, we are the first to investigate the pretreatment effect of moderate-term, endurance training before applying various dosages (10 and 20 $_{mg.kg^{-1}}$) of Adriamycin (ADR) on markers related to cardioprotection and cardiac stress in heart tissue. Our study demonstrated that although, $10_{mg.kg^{-1}}$ of ADR induced myocardial damage in rats, which was characterized by an insignificant increase in HSP_{70} and MDA, a significant increase in serum total CK and CPK-MB, and a significant decrease in SOD, a significant increase in HSP_{70} ,MDA, total CK and CPK-MB and a significant decrease in SOD were detected following $20_{mg.kg\_1}$ of ADR.

The results indicated that there is a potential relationship between oxidative stress and ADR-induced cardiac stress. In addition, these data suggested that pre-treatment with endurance regular exercise could block the increased oxidative stress caused by ADR administration, through improving antioxidants' activity. ., data from the current study also provided additional support in understanding how regular physical exercise, particularly running on a treadmill , could contribute to augmentation of cardiac muscle resistance to oxidative stress-based cardiac stress induced by ADR administration. Adriamycin/doxorubicin (DOX) is an effective chemotherapeutic agent in treating many kinds of cancers. However, its clinical application is still restricted due to its specific toxicities to cardiac tissue [1, 16]. The clinical utility of ADR is marred by an increased risk of myocardial injury, which is mainly caused by reactive oxygen species from ADR disposition [29, 30]. In other words, the possible mechanisms proposed to explain the cardiac stress effects of ADR include free radical-induced myocardial injury, lipid peroxidation and cellular toxicity [1, 30]. Because of the relatively lower levels of the antioxidant defences in the cardiomyocytes, heart is more susceptible to oxidative damage than the other tissues [30, 31, 32]. In this regard, the present study revealed severe biochemical changes as well as an oxidative damage in the cardiac tissue after treatment with $10_{mg.kg\_1}$ and $20_{mg.kg\_1}$ of ADR. The mechanism for ADR- induced cardiac stress could not be clearly understood from the present study, although a large body of evidences indicates the formation of oxygen free radicals, which can damage cells through lipid peroxidation [1, 30]. Free radicals are continuously produced in vivo and there are a number of protective antioxidant enzymes (superoxide dismutase, catalase, glutathione S-transferase, glutathione peroxidase and antioxidant glutathione) in order to deal with these toxic substances. The delicate balance between the production and catabolism of oxidants is critical in maintaining the biological functions. Two lines of evidence can be emphasized from the present study. First considering cardiac stress markers, namely MDA and CPK-MB, regular endurance training decreased the cardiac disturbances induced by administration of acute single doses of ADR, particularly, with 10mg.kg-1 dosage. Second, according to changes observed in cardiac SOD response and in part, in HSP_{70} of both control and the trained rats treated with ADR, it is likely that these markers might be considered as essential cellular defenses against free radical-based cardiotoxicity caused by ADR, providing enhanced tolerance to trained myocardium at least in the first 48 h after the end of training period. The other important finding of the present study was that after six weeks of aerobic training and ADR administration (10 or $20_{mg.kg\text{-}1}$), an insignificant decrease and an insignificant increase in $HSP_{70,}$ a significant increase in SOD of the heart tissue, an insignificant and a significant decrease in MDA, a significant increase in CPK-MB and an insignificant decrease in total CK were found, as compared to C+ADR (10 or $20_{mg.kg\text{-}1}$) groups. Moreover, although current data demonstrated that exercise could protect the heart against ADR-induced damage [24, 31]; the mechanism(s) by which exercise protects cardiomyocytes still remain unclear. There were three possible pathways to explain the protective effects of regular endurance exercise against ADR-induced cardiac stress. At present, the principal mechanism of ADR-induced cardiotoxicity is believed to be the increased oxidant production by the mitochondria [16, 24, 31, 33]. Our data indicated that ADR administration, particularly with a dose of $20_{mg.kg^{-1}}$ increased ROS production in cardiac tissue. Another interesting finding from the present study that may provide further insight into the effects of ADR on the

myocardium was a slight increase in HSP_{70} protein content in the heart of the ADR-treated rats, as compared to NT+saline group. Primary functions of HSPs include: non-training of protein folding, prevention of denaturation and aggregation of intracellular proteins during stress, acceleration of the breakdown of damaged proteins, and serving as a molecular chaperone [15, 16, 31, 34]. Other putative effects of HSP70 include protection against apoptosis, protection against oxidative damage, maintenance of cellular calcium handling, and preservation of mitochondrial integrity in cardiac tissue exposed to a variety of oxidative stressors [15, 31, 34]. Regardless of its role related to cardioprotection, HSP's overexpression can be undoubtedly interpreted as an acute sign of cellular stress [31]. Hence, given the vast protective properties of HSP70, we hypothesized that exercise -induced increases in myocardial HSP70 levels play an important role in exercise-induced cardioprotection against ADR-mediated cardiac injury [24]. Therefore, regular endurance exercise lead to a significant increase in the HSP70 and SOD activity and a decrease in lipid peroxidation in the heart tissue of T+ADR treated groups. HSP70 induction in myocardial tissue is known to occur following exercise training and is associated with the exercise-induced preservation of cardiac function during states of oxidative stress [16, 35].

Conclusion

The present study suggests that ADR treatment is associated with oxidant/antioxidant imbalance in heart tissue. In addition, the present investigation provided new insights into the biochemical mechanisms through which pre-treatment with endurance exercise training exerts its potential antioxidant properties, and protects cardiac muscle tissue against the ADR-induced toxicity. . Thus, our study suggests that six weeks of regular aerobic exercise training may be considered as a potentially useful strategy for improving myocardial tolerance against ADR-induced oxidative damage.

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