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Original Article

Aerobic training and L-arginine supplement attenuates myocardial infarction-induced kidney and liver injury in rats via reduced oxidative stress

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ABSTRACT

Introduction: The aim of the present study was to determine the effect of exercise training and l-arginine supplementation on kidney and liver injury in rats with myocardial infarction (MI).
Material and methods: Four weeks after MI, 50 male wistar rats randomly divided into five followed groups: sham surgery without MI (Sham, n = 10), Sedentary-MI (Sed-MI, n = 10) 3: L-Arginine-MI (La-MI, n = 10) 4: Exercise training-MI (Ex-MI, n = 10) and 5: Exercise and L-arginine-MI (Ex + La-MI). Ex-MI and Ex + La-MI groups running on a treadmill for 10 weeks with moderate intensity. Rats in the L-arginine-treated groups drank water containing 4% L-arginine. Tissues oxidative stress and kidney and liver functional indices were measured after treatments.
Result: Urea as a kidney function indexes, increased in Sed-MI group in compared to sham group and decreased significantly in Ex-MI and Ex + La-MI groups. The level of catalase (CAT) and glutathione stimulating hormone (GSH) of kidney were significantly lower in the MI-groups compared with the Sham group and kidney **Malondialdehyde (MDA)** levels increased after MI and significantly decreased in response to aerobic training and L-arginine. As well as, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) as liver injury indices, increased in MI-groups and decreased by training and L-arginine. In this regards, liver MDA and CAT respectively increased and decreased in MI-groups, but aerobic training and L-arginine increased liver glutathione per-oxidase (GPx) and decreased liver MDA.
Conclusion: These results demonstrated that kidney and liver function impaired 14 weeks after MI and aerobic training and L-arginine supplementation synergistically ameliorated kidneys and liver injury in myocardial infarction rats through oxidative stress reduction.

1. Introduction

The World Health Organization (WHO) has been reported that myocardial infarction (MI) is the most common cause of mortality in the world.[1] Left ventricular systolic dysfunction is the most important complication of MI. MI caused cardiac insufficiency affects not only reduces heart function but also damage to the other dependent organs such as kidneys and liver. Almost 45% of the cardiac output flows to the kidneys and liver.

It was shown that, 6 months after MI, considerable changes were observed in the rat liver.[2] MI-induced cardiac output reduction with consecutive reduction in kidneys and liver blood flow can lead to oxygen partial pressure drop in nephrons and hepatocytes.[3,4] In these regards previous studies showed that 4 weeks after induction of MI by ligation of the left coronary, the renal blood flow and the percent of cardiac output perfusing the kidneys were reduced by 18% and 14%, respectively.[5] These findings suggest close interactions between the heart and the kidney, which is known as the “cardio-renal syndrome”.[6]

Once the decrease in oxygen delivery crosses a critical threshold, a cascade of events is initiated in kidneys and liver that ultimately leads to cell deaths. It has been shown that limited cell supply and slow removal of metabolic products in the liver causes fibrosis in central vein zones, bridging fibrosis between adjacent central veins, and regeneration nodes.[2] Also, tubular atrophy, renal vasoconstriction, formation of granulation tissue,

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interstitial fibrosis, inflammation and oxidative stress are the most important outcomes of kidney tissue after MI.[4,6]

This process has been less considered in the literature and only a few case reports are documented in the scientific literature.[4,7,8] The molecular mechanism of cell deaths after MI is not yet clear. Inflammation and oxidative stress are the most common cause of damaged to the nephron and hepatocytes cells after MI.[4] Ultimately, damaged cells resulting in decreased kidneys and liver function.

In this regards, it has been shown that L-arginine as a precursor nitric oxide (NO) has various physiological properties including vasodilatation, scavenging superoxide (O^{2-}) formation and suppression xanthine oxidase (XO).[9] Previous studies showed that preservation of NO bioavailability leads to renal efferent arteriolar vasodilation, diuresis, natriuresis and increase glomerular filtration by reducing oxidative stress and maintaining renal function.[10–12] Lucas et al showed that L-arginine attenuated hepatocellular damage induced by hepatic ischemia-reperfusion in rats.[13] On the other hand, it has been shown that exercise training (ET) promotes antioxidant capacity and attenuates oxidative stress in skeletal muscle,[14] kidneys and liver[15] of rat.

In light of this information, this study was designed to evaluate the protective effect of exercise training and L-arginine in protection from oxidative stress caused by MI in kidneys and liver of rats.

2. Material and methods

2.1. Animals

Male Wistar rats (6 weeks old) weighing between 150 and 180 g were maintained in a 12 h light/dark cycle at constant room temperature 22 ± 1 °C and relative humidity 55 ± 3%. They were fed ad libitum on standard laboratory rat chow and had free access to tap water. Animals used in these experiments were treated in accordance with National Institutes of Health Guide for the Care and Use of Laboratory Animals, and the study protocols were approved by the Institutional Animal Care and Use Committee at Lorestan University of medical science. The number of approval of the ethical committee was LUMS.REC.1394.27.

2.2. Experimental myocardial infarction

Animals underwent experimental MI due to permanent left anterior decending (LAD) artery ligation or sham surgery as previously described.[16] Briefly, rats were initially anesthetized by intraperitoneally injecting of 60 mg/kg sodium thiopental, intubated via gray angiocath and initiation of ventilation (Small Animal Ventilator, Model 683, Harvard Apparatus). The heart was exposed through a left lateral thoracotomy, and ligation of the LAD coronary artery was performed using 6-0 polyethylene thread just below the tip of the left auricle. Proximal LAD artery ligation in a rat model creates a reproducibly large lateral wall infarction.

A standard limb lead-II electrocardiogram (ECG) was continuously monitored and recorded throughout the experiment, using a computerized data acquisition system (ML750 Power Lab/4sp, ADInstruments). Proper ligation of the LAD was confirmed by ST elevation and increase in R-wave amplitude in ECG. Cefazolin (25 mg/kg i.p.) was administered as preoperative antibiotic cover. After completion of all surgical protocols, the chest was re-closed with separate purse-string silk sutures (size 6–0), and the lungs were fully expanded. Body temperature was measured by rectal thermometer and maintained at 37 ± 1 °C. To ensure complete healing of the infarct zone, all rats recovered in their cages for 4 week after the operation before beginning the exercise program. The rats in the sham group underwent thoracotomy and pericardiectomy without MI.

2.3. Experimental design

Four week after the operation, 50 rats that survived randomly distributed to the following experimental groups: Sham (n = 10, Sham); sedentary-MI (n = 10, Sed-MI); exercise-MI (n = 10, Ex-MI); sedentary + L-arginine-MI (n = 10, La-MI); exercise + L-arginine-MI (n = 10, Ex + La-MI). The rats assigned to the exercise group started exercising at 4 week post-MI using a motorized rodent treadmill, while the sham and sed groups remained sedentary throughout the experiment period. Initially, all mice were habituated on a ten-channel motor-driven treadmill (Razi Rad, Iran), at a speed of 10 m/min for 10 min/day for 1 week to reduce their stress in response to the new environment. After the adaptation period, the two groups of exercised rats performed an incremental running program to obtain progressive levels of intensity (10–17 m/min, 20–50 min/day, no incline). The exercise intensity was moderate and 55–60% of maximal oxygen consumption.[17,18] To determine VO2max, as described previously,[19,20] the treadmill was placed into a metabolic chamber. Ambient air was pumped through the metabolic chamber at a flow rate of 4.5 L min^{-1}, and samples of extracted air (200 mL min^{-1}) were directed to an oxygen analyzer that was based on a paramagnetic oxygen transducer (Servomex type 1155, Servomex, UK) and a carbon dioxide analyzer (LAIR 12, M&C Instruments, The Nether-lands). The VO2max protocol involved step-wise increases in the treadmill speed as follows: a 15-min period of acclimation, after which the treadmill was started at 10 m/min and then the speed was incrementally increased 5 m/min every 3 min until the rat reached exhaustion. VO2max was measured for each animal by using three criteria: (i) no change in VO2 when speed was increased, (ii) rats could no longer keep their position on the treadmill, and (iii) respiratory quotient (RQ = VCO2/VO2) > 1. Then, based on the level of VO2max, the speed corres-ponding to 60% VO2max was determined and used for daily training for 50 min, five times a week for 10 weeks. The VO2max was measured every other week, and running speed was adjusted to maintain 60% VO2 max.

2.4. L-arginine treatment

In the entire period of investigation, subjects in the L-arginine-treated groups drank water containing 4% (w/v) L-arginine (A5006, Sigma-Aldrich, USA).[21]

2.5. Assessment of liver and kidney functions

The rats were anesthetized and sacrificed with an overdose of anesthesia 48 h after the last exercise session. Blood samples collected from the vena cava were centrifuged at 3000 rpm for 10 min for sera preparation. The sera were then stored at −80 °C and later the following parameters were measured: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), creatinine and urea. ALT and AST are markers for hepatocyte injury, ALP is sensitive markers to investigate biliary function, while creatinine and urea reflects kidney function.[22] This biochemical markers play an important role in accurate diagnosis of hepatic and renal function. The activities of blood serum marker enzymes, such as alanine transaminase (ALT), alkaline phosphatase (ALP), aspartate transaminase (AST), creatinine and urea, were measured using a Roche kit (Penzberg, Germany) and analyzed spectrophotometrically using the Hitachi Analytical Instrument (Roche Diagnostic GmbH, Mannheim, Germany).[23]

2.6. Tissue processing and homogenate preparation

The kidney and liver tissues were quickly collected and frozen in liquid N_2. Tissue homogenates were prepared at 4 °C. In brief,

tissue samples were homogenized on ice in 1 mL of ice-cold lysis buffer (10 mM NaCl, 1.5 mM $MgCl_2$, 20 mM HEPES, 20% glycerol, 0.1% Triton X-100, 1 mM dithiothreitol, pH 7.4). The homogenates were centrifuged at 1000 rpm for 10 min at 4 °C and stored at-80°C for later use.

2.7. Determination of tissues oxidative stress levels

As previously mentioned,[16] glutathione per-oxidase (GPx) activity was determined using a RANSEL kit (Randox labs), according to the method of Paglia and Valentine.[24] GPx catalyzes the oxidation of glutathione (at a concentration of 4 mmol/L) by cumene hydroperoxide. In the presence of glutathione reductase (at a concentration C0.5 U/L) and 0.28 mmol/L of NADPH, the oxidized glutathione is immediately converted to the reduced form with a concomitant oxidation of NADPH to NAD^+. The decrease in absorbance at 340 nm was measured by Hitachi U-2000 spectrophotometer. Tissue GPx activity was expressed as U/mg protein. Content of glutathione stimulating hormone (GSH) was determined in supernatant of liver homogenates by the method of Ellman (1959).[25] The proteins in samples were precipitated using 5% TCA. Supernatants were incubated with Ellman's reagent and 0.2 M potassium phosphate buffer, pH 8 for 10 min. The absorbances of the developed yellow color of samples were measured against blank at 412 nm.[26] Also, catalase activity (CAT) was measured as previously described by Aebi.[27] The decomposition of H_2O_2 was followed directly by the decrease in absorbance at 240 nm and 20 °C. Previously, tissue homogenate aliquots were centrifuged at 1000*g* and 4 °C for 10 min. The adequate amount of supernatants (60 μL equivalent to 1.5 mg tissue wet weight) was added to a reaction mixture that contained 0.002% Triton X-100, 0.1 mmol EDTA, 0.5 m potassium phosphate buffer, pH 7.0, and 15 mmol H_2O_2 in 1 mL final volume. Activity was calculated with the initial 30-s decomposition rate.

Quantification of lipid peroxidation is essential to assess the role of oxidative injury. Lipid peroxidation results in the formation of malondialdehyde (MDA) that can then be used to indicate the levels of lipid peroxidation in tissue. Lipid peroxidation products were assessed by measuring MDA level according to the method of Niehaus and Samuelsson.[28] The level of MDA in the supernatant was determined spectrophotometrically by measuring thiobarbituric acid-reactive substances with a maximum absorbance at 532 nm. Briefly, 0.5 mL of the sample was mixed with 3 mL of 1% phosphoric acid and 1 mL of 0.6% TBA solution. The mixture was heated in a boiling water bath for 45 min and cooled to the room temperature. Then, 4 mL of *n*-butanol was added, and mixture was vortexed and centrifuged at 10000*g* for 10 min. The absorbance of butanol phase (supernatant) was measured at 532 nm. Tissue MDA content was expressed as nmol/mg protein.

2.8. Statistical analyses

In order to analyze data, the SPSS statistical software version 16 was used. The data's normality test was verified by Shapiro-Wilk test. Overall group differences were analyzed using a one way ANOVA. When appropriate, post-hoc analyses were made using a Tukeys HSD test. Changes with p values lower than 0.05 were considered significant. Data are presented as mean ± SEM.

3. Results

The rate of mortality was approximately 50% during surgery and before starting of treatments. During of treatments (10 weeks) in sham, Ex and Ex + La no death was found, but in sedentary and La groups death happened in respectively 2 and 1 cases.

3.1. Kidney function

Statistical output showed that there was no significant difference in serum creatinine between experimental groups ($p = 0.06$) (Fig. 1), but serum urea was significant different between groups ($p = 0.01$). Serum urea in Sed-MI group increased more in comparison to sham group ($p = 0.02$) and significantly decreased in Ex-MI and Ex + La-MI groups in compared to the Sed-MI group ($p < 0.05$) (Fig. 2).

3.2. Kidney oxidative stress

Our statistical analyses demonstrated that there were no significant differences in GPx between treated groups, although the GPx was slightly lower in the MI rats than the sham group. GSH and CAT levels in myocardial infarction rats significantly decreased in compared to the sham group. Also, GSH and CAT levels were not significant difference between MI groups. In this regard, MDA significantly increased in response to myocardial infarction but, 10 week aerobic exercise training with and without L-arginine supplementation decreased lepid peroxidation in myocrdial infarction rat. Furthermore synergistic effect of exercise and L-arginine in MDA reduction was more in compared to the exercise alone (Table 1).

3.3. Liver function

AST was different between experimental rats groups ($p < 0.001$). AST in Sed-MI, La-MI and Ex-MI groups increased more in comparison to sham group. In these regards, AST in Ex + La-MI increased more in comparison to sham group, but these difference was not significant ($p = 0.07$). AST level in Ex + La-MI significantly decreased in compared to the other MI groups ($p < 0.05$) (Fig. 3). As well as, serum ALT level was different beteween groups ($p = 0.01$). ALT level in Ex + La-MI significantly reduced in compared to the other groups (Fig. 4). Unlike AST and ALT, serum ALP level was no significant difference between sham and MI-groups (Fig. 5).

3.4. Liver oxidative stress

As shown in Table 2, exercise and l-arginine alone have not significant effect on liver GPx level, but synergistic effect of exercise and l-arginine on GPx promotion was significant in compared to Sed-MI group.

Furthermore, statistical analyses showed that liver GSH levels were not different between experimental groups. GSH increased in response to exercise and L-arginine supplementation, but this change was not significant. On the other hand, MI significantly

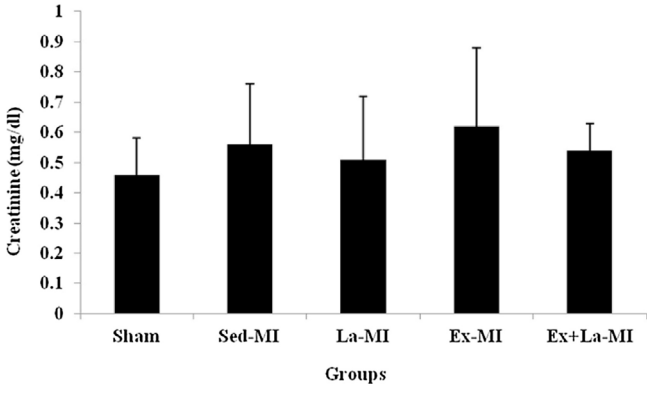

Fig. 1. No significant different of creatinine in various experimental groups.

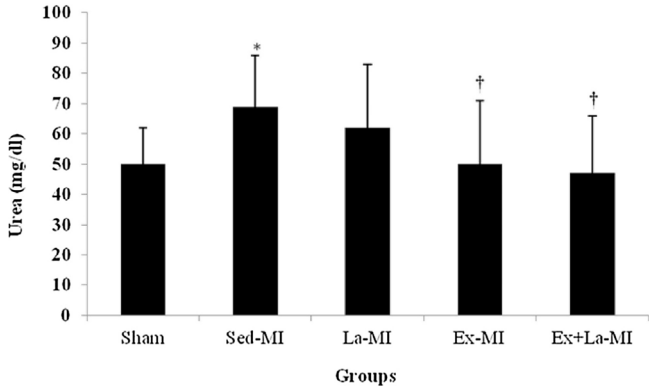

Fig. 2. Blood level of creatinine and urea in various experimental groups. * Significant difference from the Sham group at the level of $p < 0.05$, $ Significant difference from the Sedentary (Sed) group at the level of $p < 0.05$.

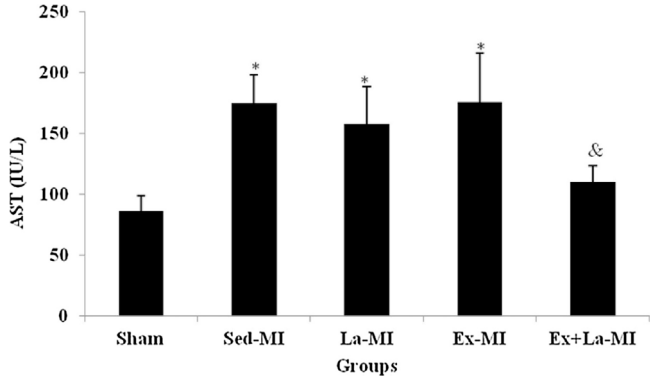

Fig. 3. Blood level of AST in various experimental groups. * Significant difference from the Sham group at the level of $p < 0.05$ & Significant difference from the Sed-MI, La-MI and Ex-MI groups at the level of $p < 0.05$.

decreased CAT level and there were no significant differences among the four MI-groups.

MDA level in myocardial infarction rats increased approximately 200%. Exercise and L-arginine have no effect on MDA reduction, but exercise and L-arginine synergistically decreased MDA in myocardial infarction rats.

4. Discussion

The influence of chronic heart failure on kidney and liver function and mechanisms and mediators underlying is not clear. In recent years, researcher are always trying to achieve effective treatment to prevent hepatocyte and renal dysfunction after MI, but their efforts has not yet impressive.

The pathophysiology mechanism(s) in cardio-renal and cardio-hepatocyte syndromes are poorly understood and likely involves interrelated concepts such as low cardiac output, increased venous congestion and venous pressure, neurohormonal and inflammatory activation, and local changes.[29]

We hypothesized that exercise training and L-arginine supplementation might favorably affect the performance of the kidney and liver after MI through amelioration of oxidative stress.

The key findings from the present study was the demonstration that (i) kidney and liver function impaired 14 weeks after MI, (ii) oxidative stress significantly increased in kidney and liver 14 weeks after MI via increase of MDA and antioxidant enzymes reduction, (iii) aerobic training with and without L-arginine supplementation ameliorated kidney dysfunction via MDA reduction, (iv) surprisingly, exercise training and/or L-arginine have no effect on GPx, GSH and CAT of kidney after MI and (v) aerobic training and L-arginine alone has no effects on liver dysfunction, but synergistically ameliorated liver dysfunction via increase of GPx and MDA reduction.

These results were in line with the results of previous studies[30,31] which reported reducing renal blood flow after chronic heart failure, increased pressure of Bowman's capsule, and increased back leakage through damaged epithelial layer of tubules also result in a severe increase in renal tissue MDA and kidney dysfunction. But the results of this study were not in agreement with Abu-Serie et al[26] that showed intraperitoneal injection of L-arginine for two weeks blocked oxidative damage of intralipid-induced steatohepatitis in liver and ameliorate liver function. A probable explanation for the difference between the results of this study and the findings of Abu-Serie related to the causative agent of oxidative stress.

One intriguing question is how aerobic exercise reduces kidney and liver injury after MI. Oxidative stress plays a major role in the pathogenesis of several kidney and liver disorders. Reactive oxygen spices (ROS) are linked to cell nephrotoxicity and hepatotoxicity. ROS promote the onset and progression of non-alcoholic steatohepatitis, that can progress to cirrhosis, with subsequent liver failure and an increased risk of hepatocellular carcinoma.[26] Oxidative stress enhances inflammation cytokine including TNF-α and increases the sensitivity of the liver to injury and necrosis and decreased liver function.[32,33] In this regards, previous studies showed that the resulting liver injury is associated with bile duct abnormality.[26]

One of the most interesting results from the current study is that exercise training and L-arginine synergistically promote renal function after MI via MDA reduction and without effect on antioxidant enzyme levels. These results are in line Marzena et al. findings that shown regular training, did not change kidney SOD, CAT or GPx activities.[34] This can be attributed to the fact that exercise training leads to decrease oxidative damage to lipids, protein and DNA by altering the rate of free radical production such as MDA, possibly via an increase in the efficiency of mitochondrial function, that is decreasing the amount of free radicals they produce without making significant changes in the amount of GPx, GSH and CAT levels.[15,35] As well, it is likely that the efficacy of the antioxidant defense system in kidney decreases after MI and unlike liver, aerobic training with moderate intensity could not revive antioxidant enzymes activity in kidneys. In these regards, previous study showed that the extent of the beneficial effect of exercise on

Table 1
Levels of kidney oxidative stress indices in various experimental groups.

Kidney	Sham	Sed-MI	La-MI	Ex-MI	Ex + La-MI
GPx	28.4 ± 4.7	25.7 ± 6.2	26.6 ± 9.3	25.4 ± 10.7	25.5 ± 5.2
GSH	8.17 ± 2.4	6.27 ± 2.0*	5.8 ± 1.8*	6.21 ± 2.9*	6.9 ± 3.1*
CAT	25.4 ± 5.9	20.5 ± 4.9*	17.6 ± 6.3*	17.8 ± 7.0*	18.8 ± 6.1*
MDA	10.7 ± 2.8	66.5.0 ± 15.2*	38.8 ± 14.9*,$	46.87 ± 17.84*,$	31.63 ± 11.91*,$,&

* Significant difference from the Sham group at the level of $p < 0.05$.
$ Significant difference from the Sedentary (Sed) group at the level of $p < 0.05$.
& Significant difference from the Exercise (Exe) group at the level of $p < 0.05$.

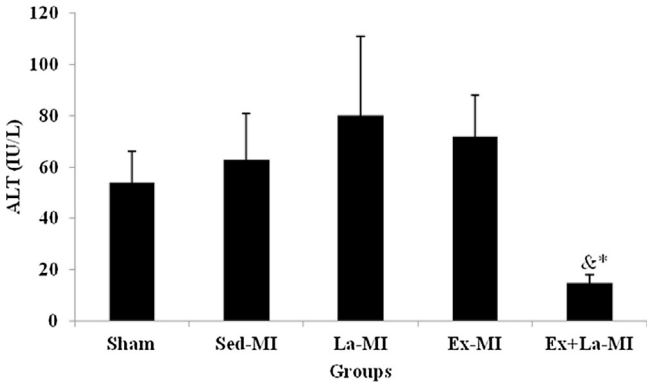

Fig. 4. Blood level of ALT in various experimental groups. * Significant difference from the Sham group at the level of $p < 0.05$ & Significant difference from the Sed-MI, La-MI and Ex-MI groups at the level of $p < 0.05$.

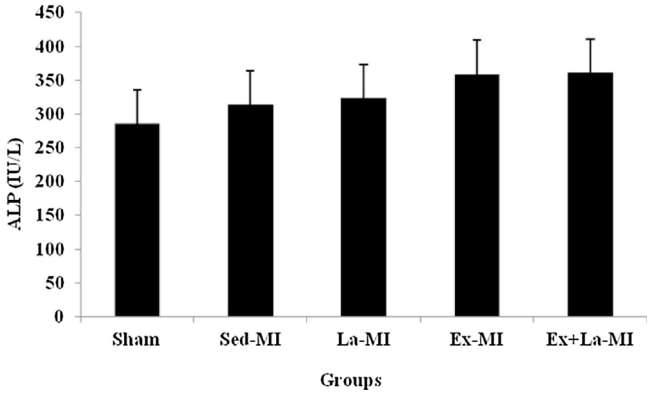

Fig. 5. No significant different of ALP in various experimental groups.

Table 2
Levels of liver oxidative stress indices in various experimental groups.

Liver	Sham	Sed-MI	La-MI	Ex-MI	Ex + La-MI
GPx	40.6 ± 11.6	38.2 ± 8.2	39.5 ± 6.0	39.9 ± 8.8	45.3 ± 10[$]
GSH	7.75 ± 1.9	8.34 ± 1.43	7.7 ± 1.7	8.32 ± 2.41	7.93 ± 1.48
CAT	37.3 ± 5.8	24.7 ± 6.8[*]	25.8 ± 9.8[*]	30.6 ± 11.6[*]	26.8 ± 8.5[*]
MDA	3.32 ± 0.6	9.68 ± 2.65[*]	8.95 ± 2.83[*]	9.95 ± 3.03[*]	2.01 ± 0.6[&]

[*] Significant difference from the Sham group at the level of $p < 0.05$.
[$] Significant difference from the Sedentary (Sed) group at the level of $p < 0.05$.
[&] Significant difference from the Sedentary (Sed), La (L-Arginine) and Exe (Exercise) groups at the level of $p < 0.05$.

oxidative stress depends not only on the type and intensity of the exercise, but also on the tissues affected.[36] These results are consistent with the other investigators who reported antioxidant enzymes were much higher in the liver than in other organs in both sedentary and training mice tissues.[37] These findings clearly indicate that antioxidant enzymes activity levels at rest and in response to training are organ-specific, although the mechanisms remain to be clarified.

As well as, angiotensin II and its receptors have a pivotal role in stimulate of intracellular formation of ROS, renal tubulo-interstitial injury and tubular cells apoptosis. It is possible that down-regulation of sympathetic system and reduced release of Ang II, followed by decreased expression of its receptors in response to aerobic training might result in kidney injury reduction, that reported by Marzena et al.[34]

On the other hand, inflammation plays a pivotal role in hypoxia-induced organ damage. It has been proven that regular exercise training decreases inflammatory cytokines.[38] Likewise, Quirino et al (2014) showed L-arginine inhibits uncontrolled synthesis of TNF-α thus block its deleterious effects.[39] It is likely that anti-inflammatory cytokine (IL-10)-mediated upregulation of anti-oxidant defenses (such as Cu/ZnSOD) via Nrf2 may represent the underlying mechanism for exercise-induced reduction of oxidative stress.[40] Taken together, exercise training and L-arginine decreased kidney and liver injury by oxidative stress reduction and probably inflammation supress, but further studies with relevant pharmacological agents are needed to clarify their association.

Our previous study also confirmed that exercise training and l-arginine resulted in stroke volume elevation in MI rats[16] and these change may increase kidneys and liver blood flow supply with subsequent kidneys and liver function promotion. Probably other contributing mechanisms such as attenuation of excessive sympathetic nerve activity[41,42] involved in exercise training-induced function amelioration of kidneys and liver in MI rats.

Aerobic training was more effective in kidney function ameliorate in comparison to L-arginine supplementation. Exercise training decreased significantly urea, but L-arginine have not effect on urea after MI. It was while, the effect of exercise training and L-arginine on kidney oxidative stress indices were similar. Also, the effect of exercise training and L-arginine on liver enzyme and oxidative stress were identical.

5. Conclusion

In conclusion, the results of these study demonstrated that kidney and liver function impaired 14 weeks after MI and aerobic training and L-arginine supplementation synergistically ameliorated kidneys and liver injury in MI rats through oxidative stress reduction.

Conflict of interest

The authors declare they have no conflict of interests.

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