Preconditioning by the exercise and curcumin protects left ventricular myocardium against ischemia-reperfusion injury and suppresses ventricular arrhythmias in rats

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Abstract

Introduction: The present study examined the effects of a 10-week preconditioning with moderate-intensity aerobic exercise and curcumin supplementation before ischemia-reperfusion (IR) to investigate if this method contributes to the protection of cardiac myocardium against IR-induced injury and left ventricular dysfunction in rat.
Materials and Methods: Male Wistar rats (6-8 weeks old) were randomly assigned to the 5 groups (each with 10 rats), sedentary-control (Sed-CON), sedentary ischemia-reperfusion (Sed-IR), exercise with IR (Ex-IR), curcumin with IR (Cu-IR), and both exercise and curcumin with IR (Ex-Cu-IR). Exercise intervention performed five times a week for 10 weeks. After the training period, arrhythmias and electrocardiogram parameters, factors involved in cardiac structure and function, and infarct size of myocardium were investigated.
Results: We observed that a 10-week moderate-intensity aerobic exercise (15-45 min at 12-24 m/min) five sessions a week as well as curcumin supplementation (50 mg/kg) over the mentioned period, in advance to IR, significantly decreased IR-induced infarct size in Ex-IR, Cu-IR, and Ex-Cu-IR groups compared to Sed-IR ($P = 0.0001$), alleviated arrhythmia by reduction in ventricular ectopic beats episodes in Ex-IR, Cu-IR, and Ex-Cu-IR groups compared to Sed-IR ($P = 0.001$), decreased ventricular tachycardia episods in Ex-IR, Cu-IR, and Ex-Cu-IR groups in comparison to that of Sed-IR group ($P = 0.001$) and improved cardiac function ($P = 0.001$).
Conclusion: According to our findings, exercise has superior cardioprotective effects than curcumin. The combination of curcumin and exercise has no preference on exercise or curcumin alone. Hence both long-term aerobic exercise and curcumin supplementation are effective cardioprotectors against IR-induced injury.

Keywords: Antiarrhythmic herbs, Cardioprotection, Moderate-intensity exercise, Reoxygenation injury, Cardiovascular disease

Introduction

As a common health problem, heart failure (HF) is a major cause of morbidity and mortality worldwide (1). Acute myocardial infarction (MI) remains one of the leading causes of HF, for which early reperfusion is currently the most effective therapy (2). Paradoxically, reperfusion itself results in additional damage, also known as myocardial ischemia-reperfusion (IR) injury (3). Myocardial injury caused by Ischemia-reperfusion is the main pathological contributing factor of myocardial infarction and HF (1). Reoxygenation injury or IR-induced injury

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is a kind of tissue damage caused by blood re-circulation to the tissue after a period of ischemia-induced decrease in oxygen supply (4). Following the restoration of coronary flow, the myocardium is susceptible to another form of damage caused by reperfusion of the previously ischemic tissue, termed reperfusion injury. Thus, the interrelation of both mechanisms of injury has been emphasized in the term IR (5). Oxidative stress is known to be a major injury mechanism implicated in the pathogenesis of ischemic myocardial injury (1). Ischemia decreases the level of nutrients and oxygen and creates a condition in which re-circulation of the blood to the tissue induces oxidative stress and causes inflammation and damage resulting in adverse myocardial remodeling (AMR) and an increased risk of progression to HF (2, 4). Hence, developing the approaches that can exhibit beneficial effects against IR-induced damage is an important goal among researchers.

An unequivocal positive relationship between physical activity and optimal health has been demonstrated with dozens of studies. It has been shown that regular exercise is beneficial for the cardiovascular system in different disease populations and different age categories (6). Exercise is not the only noninvasive and nonchemical method for the prevention of CVD. Reviewing the literature indicates vital products have attained a remarkable milestone for the treatment of cardiovascular disease (CVD). The latest increase in the fame of herbs has revived interest in conventional remedies that have been consumed in the management of CVD (7). One such herb is curcumin (diferuloylmethane), the orange-yellow and water-insoluble ingredient made from turmeric (Curcuma longa) which is extracted from the rhizome of Curcuma longa (family Zingiberaceae) (1). By scavenging various reactive oxygen species through phenolic groups in its structure, Curcumin exhibits antioxidative activities and protects the cells from oxidative damage (8).

Although several studies demonstrated anti-apoptosis, antioxidant and anti-inflammatory effects of curcumin and protective effects of the exercise, information regarding the effects of a long-term combination of moderate-intensity aerobic exercise with curcumin before IR on the post-IR injury is limited and results of studies are controversial. Moreover, the effect of such a regimen on cardiac arrhythmias is not well understood. Accordingly, the aim of the present study was to investigate the cardioprotective effects of a 10-week moderate-intensity aerobic exercise along with curcumin supplementation before IR-induced injury on IR injury, ischemia-induced arrhythmia, and cardiac morphology. We hypothesized our methods will decrease IR-induced infarct size and arrhythmia and will improve cardiac function in rats.

Materials and Methods

Animals

Fifty male Wistar rats aged 6-8 weeks (weighing 200–250g) were used. The rats were housed in large cages located in a climate-controlled room (temperature 21–24°C, humidity 40–50%) under a 12:12 light/dark cycle with food and water available at libitum. The sample size was calculated using G*Powe software (9) and five groups of rats were designated as sedentary-control (Sed-CON), sedentary ischemia-reperfusion (Sed-IR), exercise with IR (Ex-IR), curcumin with IR (Cu-IR), and both exercise and curcumin with IR (Ex-Cu-IR), each of 10. The present study was approved by the Animal Ethics Committee of Hamedan University of Medical Sciences (No. IR. BASU. REC. 1398.044), and all procedures involving animals were carries out in accordance with the ethical measures of the responsible committee on human experimentation. This research follows the institutional and

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national guide for the care and experiments on laboratory animals.

Exercise Protocol

One week before the experiment and using a motorized rodent treadmill (BIOSEB, Vitrolles, France), the rats in the Ex-IR and Ex-Cu-IR groups completed some training sessions to become oriented with the treadmill environment. Then animals were trained 5 days/week for a total of 10 weeks. Training intensity started with running at 12 m/min for 15 min/day on week 1 and was progressively increased to 24 m/min for 45 min/day (representing around 55-60% of $\dot{V}O_{2max}$) until week 7, and remained constant thereafter (Figure 1). Exercise intensity during each week was adjusted based on previously reported protocols as well as the relationship between running speed and $\dot{V}O_{2max}$ (10, 11).

Curcumin Administration

Curcumin extract (8.20354. 0010.Merck KGaA, Germany) dissolved in olive oil, and one hour before the exercise, subjects of Cu-IR and Ex-Cu-IR groups ingested daily oral gavage of 50 mg/kg of the compound.

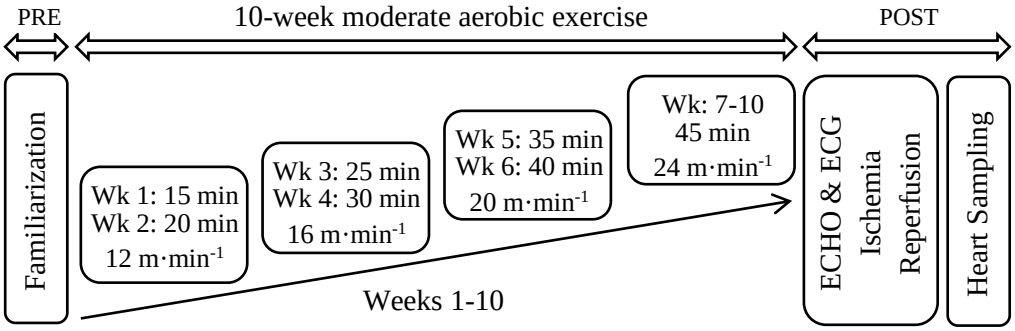


Figure 1. Overview of the experimental protocol. PRE, preexercise; POST, postexercise, Wk, week; Numbers in boxes denote volume (min) and intensity ($m \cdot min^{-1}$) of exercise bouts completed over a 10-week. ECHO, Echocardiography; ECG, Electrocardiogram.

Surgical Preparation

Myocardial infarction was inducted according to a well-established protocol (12, 13). Briefly, after intraperitoneal anesthesia (ketamine 60-80 mg/kg and xylazine 8 mg/kg), mechanical ventilation (Harvard Model 683, USA), and intubation, thoracotomy was performed in the left hemithorax of each animal. Once the heart was exteriorized, the left anterior descending coronary artery was ligated using 6-0 polyethylene thread.

After rapid repositioning of the heart, the chest was closed following lung hyperinflation. The animals of the Sed-CON group underwent the same surgery, but without coronary ligation. Diagnostic confirmation of myocardial infarction was performed by echocardiography and ST-segment elevation was deemed as the symbol of ischemia which was recorded by ECG. Five days after myocardial reperfusion, the rats underwent a second surgery and the heart was excised, rinsed with normal saline, and weighed on the digital scale after the atria and great vessels were dissected away. Then, the left ventricular (LV) myocardium was harvested from the heart, immediately frozen in liquid nitrogen, and stored in an RNase-free microtube at −80°C.

Determination of Myocardial Infarct Size

The cardiac infarct area was evaluated using TTC (Sigma, St. Louis, MO, USA) staining. The frozen heart was cut into 3 mm sections and stained with 1% 2, 3, 5-triphenyltetrazolium chloride solution (TTC; in 0.1 M phosphate buffer; pH=7.4) for 15 minutes at 37°C to visualize the infarct zone and were subsequently fixed in 10% formalin for 24 hours. TTC stained areas were analyzed by Adobe Photoshop software (version 7.0, Adobe Systems).

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Finally, myocardial infarct size was reported as a percentage of the LV area (Figure 2).

Determination of Arrhythmias and Electrocardiogram Parameters

Ventricular arrhythmias were evaluated during the 30-minute ischemia period. Identifiable premature QRS complex indicated ventricular ectopic beats (VEBs). A run of four or more ventricular premature beats indicated ventricular tachycardia (VT) and ventricular fibrillation was identified as a signal for which individual QRS deflections cannot be separated from each other for which a rate could no longer be measured (14). Arrhythmias severity was identified as per the previously mentioned scoring system and according to its incidence, onset time, and duration (15). The duration of QRS interval, corrected QT interval (QTc), the amplitude of T and R and the elevation of ST-segment were recorded at the baseline, end of 30 min ischemia, and 60 min of reperfusion. Starting point from the onset of QRS complex until the end of T wave identified as QT interval. QTc was calculated using the following equation (14):

$QTc = QT/\sqrt{RR}$

Doppler Echocardiography

5 days after reperfusion and using the same previously mentioned anesthetic regimen, Doppler echocardiographic was performed in anesthetized rats. The procedures were performed by an observer blinded to the groups to which the animals had been assigned. According to the previously described methodology, a 12 - MHz transducer was used in depth between 2 and 3 cm using Sonos 5500 equipment (Philips Medical System, Andover, MA, USA). The animals were placed in the left lateral position following thorax shave. Then the images were recorded and the final result was obtained from the mean of three different cardiac cycles. Also, the resting Echocardiography parameters like septal dimension (SEPd), LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV), LV end-diastolic dimension (LVEDd), and LV end-systolic dimension (LVESd) were measured. LVESd and LVEDd were calculated using the following equations (16):

$LVESV = 7\ LVESd^3/ [2.4 + LVESd]$, $LVEDV = 7\ LVEDd^3/ [2.4 + LVEDd]$.

Stroke volume (SV), LV ejection fraction (EF), and LV fractional shortening (FS) were calculated using the following equations (17):

$SV = (LVEDV – LVESV)$; $EF = (LVEDV - LVESV)/LVEDV$; and $FS (\%) = [(LVEDd – LVESd)/LVEDd] \times 100$.

Results

Characteristics of the Experimental Groups

Table 1 indicates post-treatment characteristic of the experimental groups. No significant difference was observed between groups for body weight ($P = 0.9$) and heart-to-body weight ratio (g/g) $\times 10^2$ ($P = 0.09$) following the experiment. A significantly higher heart weight (g) was observed in the Ex-Cu-IR group compared to the Sed-CON ($P = 0.002$), Sed-IR ($P = 0.004$), and Cu-IR ($P = 0.002$) groups.

Infarct Size

In comparison to the Sed-IR group, Ex-IR, Cu-IR, and Ex-Cu-IR groups showed significantly lower infarct size (43.28 ± 2.71% vs. 15.26 ± 0.77%; 20.65 ± 1.35%; 15.62 ± 0.85%, respectively). Also, infarct size in Ex-IR and Ex-Cu-IR groups was lower when compared to that of Cu-IR ($P = 0.035$, and 0.046, respectively).

Echocardiographic Data

As shown in Table 2, there were no significant differences among the experimental groups in LVEDd, SEPd, LVEDV, and SV. Values of LVESd and LVESV were significantly ($P = 0.001$) greater and values of FS and EF were significantly lower ($P = 0.001$) in Sed-IR

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compared to those of the Sed-CON group. Also, LVESd and LVESV were significantly (P = 0.001) lower and FS and EF were significantly greater (P = 0.001) in Ex-IR, Cu-IR, and Ex-Cu-IR groups compared to those of the Sed-IR group.

Table 1. Post-treatment characteristics of the experimental groups (each group comprised of 10 rats) under study.

Characteristic	Sed-CON	Sed-IR	Ex-IR	Cu-IR	Ex-Cu-IR
Body weight (g)	295.67 ± 14.13	287.75 ± 12.63	290.67 ± 16.61	290.17 ± 14.03	304 ±15.08
Heart weight (g)	**0.88 ± 0.05	**0.90 ± 0.04	0.98 ± 0.09	**0.88 ± 0.09	1.05 ± 0.03
Heart-to-Body weight (g/g) × 10^2	0.30 ± 0.02	0.31 ± 0 .01	0.34 ± 0.05	0.30 ± 0.02	0.35 ± 0.04

Sed, sedentary; IR, Ischemia-Reperfusion; Ex, Exercise; Cu, Curcumin.

**Significant difference compared to Ex-Cu-IR (P < 0.01).

Table 2. Echocardiographic assessment of left ventricular in different experimental groups of rats showing the post-treatment cardiac function.

Parameters	Sed-CON	Sed-IR	Ex-IR	Cu-IR	Ex-Cu-IR
LVEDd (mm)	4.3 ± 0.13	4.67 ± 0.12	4.57 ± 0.26	4.67 ± 0.05	4.66 ± 0.10
LVESd (mm)	2.12 ± 0.11	3.28 ± 0.08*	2.34 ± 0.07#	2.47 ± 0.11#	2.36 ± 0.09#
SEPd (mm)	1.52 ± 0.08	1.44 ± 0.05	1.51 ± 0.16	1.47 ± 0.20	1.49 ± 0.15
FS (%)	50.24 ± 3.23	29.81 ± 0.44*	48.08 ± 2.96#	47.21 ± 2.01#	49 ± 3.05#
LVEDV (µL)	199.07 ± 17.19	251.29 ± 19.33	243.3 ± 37.14	247.27 ± 8.49	248.8 ± 14.47
LVESV (µL)	26.27 ± 3.83	93.26 ± 7.73*	34.06 ± 3.07#	40.89 ± 5.11#	35.77 ± 4.29#
EF (%)	86.1 ± 2.42	62.98 ± 0.45*	84.46 ± 2.24#	83.55 ± 1.75#	84.89 ± 2.69#
SV (µL)	172.8 ± 19.02	158.04 ± 11.68	209.23 ± 36.42	206.38 ± 7.08	213.03 ± 18.40

Values are as Mean ± SEM. IR, Ischemia-Reperfusion; Ex, Exercise; Cu, Curcumin; LVEDd, left ventricular end-diastolic dimension; LVESd, left ventricular end-systolic dimension; SEPd, septal dimension; FS, fractional shortening; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end- systolic volume; EF, left ventricular ejection fraction; SV, stroke volume.

*Significant difference compared to the Sed-CON group; # Significant difference compared to the Sed-IR.

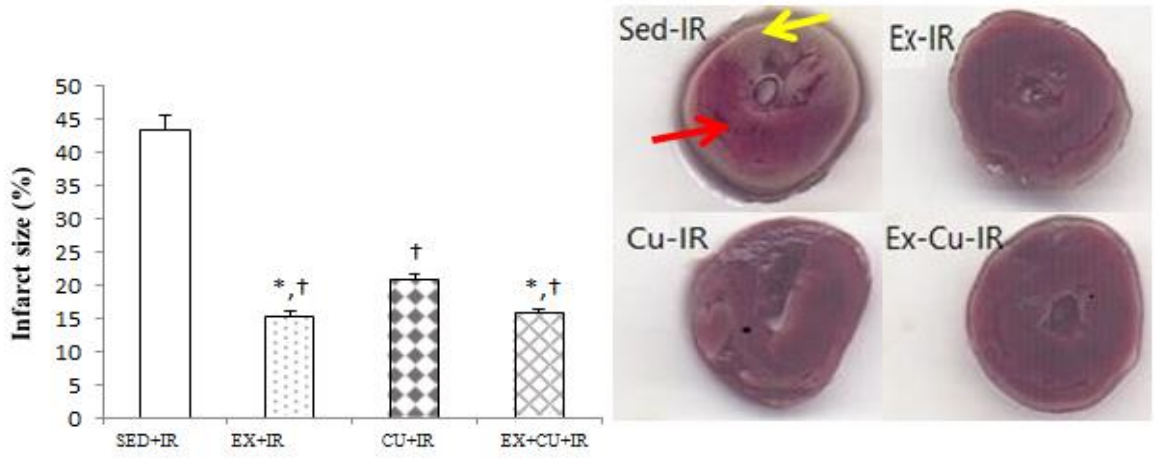


Figure 2. Percentage of infarct size in the experimental groups. Bar chart indicates percentage of infarct size in different groups and colored segments visualize an example of the infarct area. Sed, sedentary; IR, Ischemia Reperfusion; Ex, Exercise; Cu, Curcumin. †Indicates significant difference compared to Sed+IR group. *Indicates significant difference compared to Cu+IR group. Yellow arrow indicates infarct area (pale pink or white) and red arrow indicates non-infarct area (red).

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Ventricular Arrhythmias during Ischemia

Figure 3 (A and B) shows the total number of VEBs and VT. The mean total number of VEB episodes during 30-min of ischemia in Ex-IR, Cu-IR, and Ex-Cu-IR groups markedly reduced compared to the Sed-IR group (33.11 ± 4.99, 42.23 ± 6.51, 37.61 ± 4.97 vs. 75.50 ± 5.79, respectively). Also, exercise and curcumin administration reduced total number of VT episods in Ex-IR, Cu-IR, and Ex-Cu-IR groups compared to Sed-IR group (3.1 ± 0.31, 5.7 ± 0.30, 4.0 ± 0.36 vs. 8.50 ± 0.36, respectively).

Figure 3C shows mean total duration of all VT episodes. Duration of VTs throughout 30-min of ischemia was significantly (*P* = 0.001) reduced in Ex-IR, Cu-IR, and Ex-Cu-IR groups (71 ± 7.23 s, 252 ± 12.64 s, 163 ± 11.08 s, respectively) when compared to that of Sed-IR group (372 ± 28.54 s). VT time was significantly greater in Cu-IR group compared to that of Ex-IR and Ex-Cu-IR groups (P = 0.001, and 0.01, respectively). Also, Ex-Cu-IR showed longer VT longer VT episode when compared to Ex-IR (P = 0.01).

Other ECG Parameters

The ECG analysis showed remarkable variation, including QTc interval shortening in Cu-IR and Ex-Cu-IR groups (*P* = 0.001) and lengthening of this variable in Sed-IR and Ex-IR (*P* = 0.01, and 0.001, respectively) at the end of ischemia period compared to baseline. Also, QTc interval at the end of ischemia was significantly shorter in Cu-IR and Ex-Cu-IR groups compared to Ex-IR group (*P* = 0.01, and 0.001, respectively). It is worth mentioning that, at the baseline, value of QTc in Ex-IR group was significantly lower than that of the other groups (P = 0.001).

QRS interval significantly decreased in Ex-Cu-IR group (P = 0.001) and increased in Sed-IR group (P = 0.001) as compared to the baseline. Following the ischemia, the value of QRS was significantly lower (P = 0.001) in three experimental groups compared to that of Sed-IR. R-wave significantly (P = 0.001) was lower in all three experimental groups compared to Sed-IR. R-wave was significantly greater in Cu-IR (P = 0.01) and Ex-Cu-IR (P = 0.05) groups as compared to that of Ex-IR group. Also, this variable significantly (P = 0.001) decreased in Ex-IR group at the end of ischemia compared to baseline. At the end of ischemia, repolarization voltage (T-wave) significantly increased in Ex-IR group compared to Cu-IR, Ex-Cu-IR, Sed-IR (P = 0.01, 0.01, and 0.001, respectively), and its baseline (P = 0.001). The mean value of ST segment voltage was significantly lower in three experimental groups compared to Sed-IR group.

At the end of reperfusion period, QTc interval significantly (P = 0.001) shortened in Cu-IR and Ex-Cu-IR groups compared to the baseline. QTc duration was significantly lower in all three experimental groups (P = 0.001) as compared to Sed-IR with the significantly (P = 0.001) lower QTc interval in Ex-IR in comparison to the end of the ischemia.

QRS interval in Ex-IR and Ex-Cu-IR was significantly lower (P = 0.001, 0.05, respectively) compared to that of Sed-IR. Also, value of this variable increased in Ex-Cu-IR group compared to the end of ischemia (P = 0.01).

R-wave was significantly lower in all experimental groups compared to that of Sed-IR (P = 0.001). Also, value of this variable significantly (P = 0.01) decreased in Ex-IR group compared to the baseline.

T-wave was significantly greater in Ex-IR group compared to Sed-IR (P = 0.01), Cu-IR (P = 0.001), and Ex-Cu-IR (P = 0.05) groups, but lower than its own baseline (P = 0.01). The mean value of ST segment voltage was significantly lower (P = 0.001) in all three experimental groups compared to Sed-IR group.

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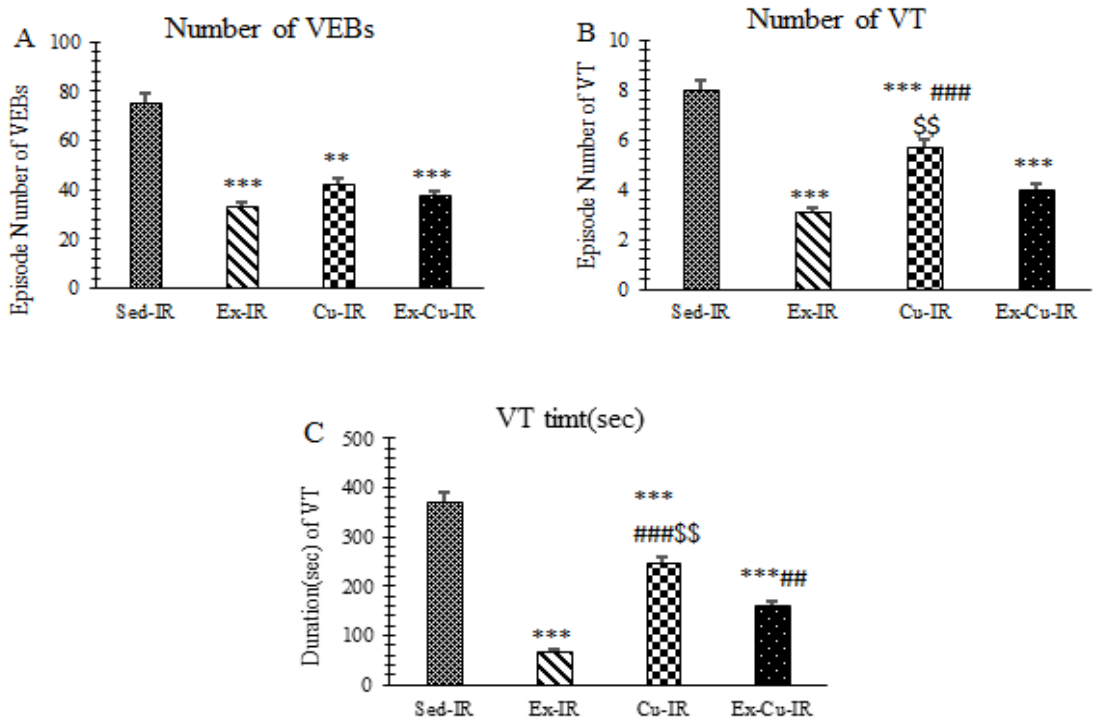


Figure 3. Ventricular arrhythmias during ischemia. (a) ventricular ectopic beats (VEBs) and (b) the total number of ventricular tachycardia (VT) during 30-min ischemia in different groups. (c) Duration (s) of VT during 30-min ischemia in different groups. Data are presented as mean ± SEM. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ versus Sed-IR group, $^{\#\#\#}P < 0.001$ versus Ex-IR and $^{\$\$}$ $P < 0.01$ versus Ex-cu-IR group.

Table 3. Echocardiographic parameters in different experimental groups of rats under study at the baseline, the end of ischemia and the end of reperfusion.

Time	Variable	Sed-IR	Ex-IR	Cu-IR	Ex-Cu-IR
Baseline	QTc(ms)	230.94 ± 5.37	100.77 ± 7.35$^{\#}$	214.98 ± 8.70$^{£}$	210.1 ± 10.25$^{£}$
	QRS (µV)	17.21 ± 0.41	15.87 ± 0.86	18.71 ± 0.35$^{£}$	17.66 ± 0.64
	R(µV)	495.87 ± 28.72	380.26 ± 30.59$^{\#}$	432.83 ± 27.95	400.7 ± 31.11
	T(µV)	261.68 ± 16.10	243.15 ± 18.02	219.05 ± 19.64	232.27 ± 15.24
	ST (µV)	263.4 ± 15.46	158.13 ± 22.03$^{\#}$	201.83 ± 18.33	169.45 ± 27.08$^{\#}$
End of ischemia 30min	QTc(ms)	267.19 ± 8.19*	149.18 ± 3.91$^{\#}$*	110.31 ± 6.7$^{\#£}$*	102.66 ± 8.32$^{\#£}$*
	QRS (µV)	20.6 ± 0.51*	14.29 ± 0.75$^{\#}$	17.11 ± 0.54$^{\#£\&}$	13.88 ± 0.40*$^{\#}$
	R(µV)	625.94 ± 41.45	221.83 ± 17.78*$^{\#}$	397.18 ± 47.34$^{\#£}$	385.57 ± 23.95$^{\#£}$
	T(µV)	242.22 ± 17.13	368.74 ± 20.72*$^{\#}$	263.62 ± 18.83$^{£}$	270.1 ± 17.26$^{£}$
	ST (µV)	315.2 ± 20.7	182.92 ± 24.39$^{\#}$	226.14 ± 17.80$^{\#}$	203.81 ± 16.87$^{\#}$
End of reperfusion 60min	QTc(ms)	236.14 ± 7.77	105.83 ± 7.17$^{\#\$}$	124.97 ± 11.67$^{\#}$*	121 ± 9.24$^{\#}$*
	QRS (µV)	18.91 ± 0.61	14.97 ± 0.72$^{\#}$	17.21 ± 0.64	16.32 ± 0.32$^{\$\#}$
	R(µV)	547.02 ± 42.96	261.08 ± 22.47*$^{\#}$	347.34 ± 33.89$^{\#}$	338.27 ± 18.87$^{\#}$
	T(µV)	253.76 ± 19.22	352.78 ± 21.39*$^{\#}$	214.59 ± 22.61$^{£}$	269.06 ± 14.93$^{£}$
	ST (µV)	306.52 ± 21.7	127.86 ± 13.61$^{\#}$	189.97 ± 15.31$^{\#}$	171.19 ± 15.87$^{\#}$

Values are as Mean ± SEM. *Significant difference compared to its baseline; $^{\#}$Significant difference compared with Sed-IR group; $^{£}$Significant difference compared with Ex-IR group; $^{\$}$Significant difference compared with the end of ischemic period; $^{\&}$Significant intergroup differences compared with Ex-Cu-IR group.

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The majority of studies to date have implemented these methods following IR, whereas this study investigated influence of the mentioned regimens before IR. The major findings from this study were that 10 weeks of aerobic exercise along with curcumin supplementation significantly decreased IR-induced injury as evidenced by infarct size in the myocardium of rats. Also, the employed protocols decreased cardiac dysfunction through reduction in episodes of VTs and VEBs and total duration of VTs, decrease in ST segment changes, QTc shortening, and decreased the R-wave amplitude.

Consistent with previous studies that have confirmed cardioprotectvie effects of curcumin through alleviation of oxidative stress and apoptosis inhibition (1, 18), subjects of our experimental groups revealed significantly lower infarct size compared with the Sed-IR group. Also, infarct size of both Ex-IR and Cu-Ex-IR groups was significantly lower than that of the Cu-IR group indicating superior protective effects of the exercise. Our findings support Ma et al. who reported decrease in infarct size and myocardial apoptosis following supplementation of 100 mg/kg/day curcumin one week prior to IR (19).

These researches attributed lower infarct size to reduced reactive oxygen species and Malondialdehyde, and increased nuclear factor erythroid 2-related factor 2, and Superoxide dismutase.

In another ex vivo study on rats, it has been reported that administration of 200 mg/kg/day curcumin for seven days before IR, attenuates oxidative stress and mitochondrial dysfunction through the inhibition of apoptosis and autophagy (20). Although in these experiments dosage of curcumin was higher than our regimen, the duration of curcumin supplementation was longer in our experiment which could justify of the same outcomes. In one in vivo study, Nahrendorf and colleagues showed that lower doses of daily curcumin administration (10, 20, and 30 mg/kg, by oral gavage for 20 days before IR) improves myocardial function and attenuates heart damage by extracting through its antioxidative and antiapoptotic effects (21). Overall, curcumin can protect cardiomyocytes against apoptosis-related cardiac diseases by diminish in infarct size through activating PI3K, Akt, ERK1/2 and Bcl-2 expression; suppressing JNK, p38 MAPK, Bax and caspase-3 which is mediated by the JAK-2 and JAK2/STAT3 signaling pathway (22).

On the other hand, several studies have demonstrated that regular bouts of exercise training before IR is capable to confer cardioprotection (23, 24) which is supportive of our findings. By contrast, several numbers of the studies which examined healing effects of exercise following IR (25, 26, 27) demonstrated no effects on infarct size. Ghahremani et al. indicated that IR-induced infarct size can be decreased following 8 weeks of aerobic exercise through regulation of mitochondrial fusion and fission and improvement of mitochondrial dynamics (23). Brown et al. showed that long-term aerobic exercise protects the heart against IR injury and decreases infarct by better maintenance of coronary flow and mechanical function after ischemia-reperfusion (24). By contrast, Nunes et al. reported that in response to 8 weeks of aerobic exercise performed at a speed of 16 m/min (5 sessions per week) after IR, despite improving heart function, the size of infarction area did not change in Wistar rats (25). Likewise, de Waard et al. reported no change in the infarct size in response to 8 weeks of aerobic exercise following myocardial infarction (26). In another experiment, Ranjbar et al. showed that ten weeks of aerobic endurance exercise performed at the intensity of 55-60% of $\dot{V}O_2max$ did not change the size of infarction in myocardium of male rats (27). With the interpretation of the aforementioned studies, we can only speculate that the preconditioning may be an effective method that improves

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resistance of myocardium against IR-induced injury causing to lowered size of infarction. Collectively, increased antioxidant capacity, increased levels of heat shock proteins, altered nitric oxide signaling pathway, enhanced function of K_{ATP} channels, and increased activation of the opioids system are proposed cardioprotective mechanisms provided with the exercise (28).

Other important adaptations after the training period were improved cardiac structure and prevented arrhythmias. Improved cardiac morphology and function were in line with the earlier studies which reported positive effects of both curcumin (1, 18) and the exercise (17, 23). There was no between-group difference among the three experimental groups for morphological variables indicating no superior effects of the regimens. Also, our results showed that both exercise and curcumin markedly lowered the number of VEBs and VT and significantly shortened VT time. Lower values of VT number and VT time in Ex-IR and Ex-Cu-IR groups are supportive of superior effects of the exercise as compared to curcumin. QT interval prolongation has been proposed as a risk factor for ventricular arrhythmia and death in patients after myocardial infarction. As we mentioned, the anti-arrhythmic properties of curcumin extract in the present study were associated with a significant decrease of QTc interval. In line with our findings, Song and colleagues indicated that curcumin acts as a multi-ion channel blocker and reduces the occurrence of VT in animals subjected to IR (29). In addition to direct effects on the ion channels that maintain the action potential of ventricular myocytes, indirect mechanisms such as central nervous and autonomic regulations and electrolyte changes are effective in QT interval changes (30). On the other hand, and in support of our hypothesis, studies repeatedly documented cardioprotective effects of the exercise in animal models as exercise confers resistance against several different indexes of ischemia-reperfusion injury including infarction (31), myocardial stunning (32, 33), and arrhythmia (34, 35). Aerobic exercise alters autonomic balance by increasing parasympathetic tone and decreasing sympathetic activity and enhances cardiac electrical stability in a nonpharmacological way (34). Moreover, maintained glutathione environment through heightened glutathione reductase activity appears to be involved in the exercise-induced protection against arrhythmia (35).

Conclusion

In summary, this study demonstrates that performing a 10-week moderate aerobic exercise protocol (15-45 min at 12-24 m/min) five sessions a week as well as curcumin supplementation (50 mg/kg) over the mentioned period before IR, decreased IR-induced infarct size, alleviated arrhythmia by enhancing cardiac electrical stability and improved cardiac morphology and function. Results of our experiment indicate exercise has superior cardioprotective effects than curcumin. The combination of curcumin and exercise has no preference on exercise or curcumin alone. Hence both long-term aerobic exercise and curcumin supplementation are effective cardioprotectors against IR-injury.

Authors' contribution

All authors contributed equally to this study.

Conflict of interest

The authors declare that they have no conflict of interest.

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