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# Role of 12-week resistance training in preserving the heart against ischemia--reperfusion-induced injury

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## Abstract

**Background:** *Discovering an effective approach to provide cardioprotection against coronary artery disease has long been sought. We studied the cardioprotective effect of resistance training against ischemia-reperfusion-induced injury.*

**Methods:** *Twenty male rats were divided into trained and sedentary groups (n = 10 in each). The rats were exercised in squat-training apparatus (12 repetitions/set, four sets/day and five days/week for 12 weeks). After the last training session, transient regional ischemia of left anterior descending coronary artery (40 min) was followed by 80 min of reperfusion. Coronary flow, left ventricular developed pressure, diastolic pressure and infarct size were measured.*

**Results:** *After 35 min of ischemia, coronary flow and developed pressure were higher in trained than untrained groups (10.37 ± 0.96* vs *7.54 ± 0.89 mL/min × g, p < 0.01 for coronary flow and 67.74 ± 3.31* vs *52.39 ± 4.28 mm Hg, p < 0.01 for developed pressure) and this difference persisted until 50 min of reperfusion (10.59 ± 0.88* vs *7.71 ± 0.73 mL/min × g, p < 0.01 for coronary flow and 58.12 ± 4.07* vs *39.56 ± 3.79 mm Hg, p < 0.01 for developed pressure). Diastolic pressure was significantly lower from 35 min of ischemia (11.51 ± ± 5.37* vs *24.53 ± 5.44 mm Hg, p < 0.05) through 35 min of reperfusion in trained rather than sedentary rats (30.62 ± 3.19* vs *43 ± 7.11 mm Hg, p < 0.01). Resistance exercise training reduced the infarct size statistically in trained rats as compared with sedentary animals (39.32 ± 4.09* vs *29.36 ± 4.17 percentage of zone at risk, p < 0.05).*

**Conclusions:** *These results show that chronic resistance exercise provides cardioprotection against myocardial injuries.* (Cardiol J 2011; 18; 2: 140–145)

**Key words: exercise, heart, infarction, ischemia, reperfusion**

## Introduction

Coronary artery disease is a leading cause of death worldwide. The main pathological manifestation of coronary artery disease is myocardial damage due to ischemia-reperfusion injury [1]. Clinically, myocardial ischemia-reperfusion relates to conditions such as myocardial infarction, coronary angioplasty, thrombolytic therapy, coronary revascularization and heart transplantation [2]. Many approaches to

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provide cardioprotection against ischemia-reperfusion-induced injury have been studied. Until now, regular exercise has been agreed to be a pragmatic and sustainable countermeasure for cardioprotection [3–10]. While convincing evidence indicates that both short-term (three to five consecutive days) and long-term (months) endurance exercise training (i.e. running and swimming) improves myocardial tolerance to ischemia-reperfusion-induced injury in both male and female animals as well as young and old animals [1], the cardioprotective effects of resistance exercise training (such as body building and weight-lifting) against ischemia-reperfusion-induced injury have not been examined. Resistance exercise training is a specialized method of conditioning designed to increase strength and muscle endurance [11]. Similarly, it has been shown that resistance training has beneficial effects on some physiological and pathological processes such as physical fitness, quality of life and chronic heart failure [3–5]. While the risk of cardiovascular (CV) complications is the primary concern with resistance training in some cardiac patients (due to blood pressure elevation during this type of exercise), resistance training can also increase muscle strength and endurance and can positively influence quality of life, CV risk factors and CV function in healthy persons and in selected patients with CV disease [6, 7, 12, 13].

Although several investigators have studied the impact of resistance training on cardiac structure and function, to the best of our knowledge there has been no publication looking at the cardioprotective effect of resistance exercise training against ischemia-reperfusion-induced injury. The present study investigates cardiac performance and cardiac infarct size after ischemia-reperfusion-induced injury in rats undergoing resistance exercise training for 12 weeks.

## Methods

### Animals

Twenty male Wistar rats (three months old and with a body mass of 218 ± 14 g) were obtained from the laboratory animal house of Tabriz University of Medical Sciences and randomly divided into trained and sedentary groups (n = 10 in each group). Animals were housed at room temperature (23 ± 2°C) with 12 hour light/dark cycles and had free access to food and water. The study protocol was designed in accordance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication, revised 1996) and approved by the Ethics Committee for the Use of Animals in Research of the Tabriz University of Medical Sciences.

### Training program

Trained rats were exercised according the model described by Tamaki et al. [14], with some modification. Rats were placed vertically in a squat-training apparatus cylinder (RatWLI009, Tajhiz Azmaye Pooya Co, Iran) where they could stand on their hind legs in response to electrical stimulation and raise the piston located above their heads. An electrical stimulation (20 V, 0.3 s duration at 3 s intervals) was applied to the rat's tail through a surface electrode. After one week of adaptation, the trained group of rats exercised four sets of 12 repetitions per day, with a 90 s rest period between each set, five times per week for 12 weeks [11]. Each rat in the trained group was weighed daily and 120% of its body weight (approximately 70% of maximum load that the rats were able to raise following electrical stimulation) was considered the weight of the piston. The piston movement for each rat was recorded by a distance sensor positioned above the piston and the work performed by each rat was calculated daily by multiplying the piston weight by the piston movement.

### Heart preparation

Adhering to the method of Brown et al. [15], after anesthetization with pentobarbital sodium (35 mg/kg ip injection) the hearts were excised, placed in ice-cold saline, and rapidly hung by the aorta on the cannula of Langendorff apparatus. Hearts were perfused with 37.5°C Krebs buffer (76.5 mm Hg perfusion pressure with 95% $O_2$ and 5% $CO_2$) containing 117.4 mM NaCl, 4.7 mM KCl, 1.9 mM $CaCl_2$, 1.2 mM $MgSO_4$, 1.2 mM $KH_2PO_4$, 5 mM pyruvate, 11 mM glucose, 0.5 mM EDTA, 25 mM $NaHCO_3$ and 1200 U/L heparin. A pressure-transducing catheter was placed through the cannula and aortic valve into the chamber of the left ventricle, and developed pressure was acquired with a computer connected to the transducer (PowerLab, AD Instruments, Australia). After five min stabilization period, baseline pressure was measured, and coronary flow rate was obtained by collecting the coronary effluent for one min.

### Ischemia-reperfusion protocol

After baseline had been recorded, a suture was threaded through the left anterior descending coronary artery 3–5 mm distal to the aorta. Both ends of the suture were inserted into a small polyethylene tube that was used as a snare, and ischemia was

induced by tightening the snare so that the artery was fully compressed. Pressure and coronary flow measurements were recorded five, 15, and 30 min after onset of ischemia. After 40 min, the snare was loosened, and reperfusion ensued for 80 min. Coronary flow and pressure data were recorded five min after the onset of reperfusion and then every 15 min until the end of the 80 minute reperfusion period.

## Measurement of infarct size

Infarct size was measured using methods similar to those previously described [15]. After the reperfusion period, the snare was re-tightened around the left anterior descending coronary artery, and 100 $\mu$L of 0.05% Evans blue solution was injected into the aortic cannula and for three min perfused through the heart. Then the heart was sliced transversely from base to apex into four slices of equal width. Each slice was immersed in phosphate buffer and was photographed with a digital camera. After both sides of each slice were photographed, each slice was placed in 100 mM phosphate buffer with 0.1% triphenyltetrazolium chloride and incubated for 10 min at 37°C. After incubation, each side of every slice was again photographed, and the slices were weighed. Heart weight was obtained by adding together the slice weights for each heart. To avoid experimenter bias, images of the slices were analyzed in a single-blind manner by Scion Image 4.0 software. Total slice area, zone at risk (ZAR) (the area of each slice that did not turn blue after perfusion with the solution containing Evans blue dye), and infarct area (the portion of the ZAR that did not turn red in response to triphenyltetrazolium chloride incubation and remained white) were measured. The ZAR and the infarct area were obtained from each side of a single slice, and the mean of both sides was used as the representative ZAR and infarct area for that slice.

Finally, the infarct area was expressed as a fraction of all ZAR by taking the sum of all infarcts and was reported as a percentage.

## Exclusion criteria

Data was omitted from analysis if: unclear resolution of heart slice images precluded analysis of infarction (n = 1); or if coronary flow did not decrease at the onset of ischemia or increase at the onset of reperfusion (n = 2); or if hearts did not complete the ischemia-reperfusion protocol due to fibrillation (more than one minute) or technical difficulty (n = 1).

**Table 1.** Effects of resistance exercise on rat's morphology.

| | Sedentary | Trained |
|---|---|---|
| Body weight [g] | 298 ± 17 | 277 ± 15 |
| Heart weight [g] | 0.90 ± 0.04 | 1.05 ± 0.08* |
| Body/heart ratio | 2.9 ± 0.19 | 3.5 ± 0.20** |
| Baseline HR [bpm] | 245.2 ± 24.99 | 213.5 ± 25.61* |

Values are mean ± SD (n = 10 rats); *,**: $p < 0.1$ and $p < 0.05$ as compared to the sedentary group; HR — heart rate

## Data analysis

All statistical comparisons were made using SPSS 16.0 software (Chicago, IL, USA) and were expressed as mean ± SE. Work performed, pressures and flow data were analyzed using repeated measures ANOVA. When a significant p-value was obtained, a post hoc Bonferroni test was employed to determine the differences between the groups. Between-group comparisons of heart rate, infarct size, body weight and heart weight were made using a Student's *t*-test. A p-value of $< 0.05$ was considered statistically significant.

# Results

## Morphology

Morphological data from trained and sedentary rats are presented in Table 1. There were no statistical differences in body weight between the groups. But the rats in the trained group had significantly greater heart weight and lower baseline heart rate than the sedentary group ($p < 0.01$). The heart to body weight ratio, as an index of heart hypertrophy, was greater in trained than in sedentary rats ($p < 0.05$).

## Work performed

Figure 1 shows a progressive increase in the weight-lifting ability of trained rats. Both the sedentary and trained groups had similar values for work performed in the beginning (week 1) of the protocol. The work performed from week 2 through week 12 was significantly greater in trained rats than the sedentary group ($p < 0.01$).

## Coronary flow rate and left ventricular pressures

Baseline values for developed pressure, diastolic pressure and coronary flow were similar in the two groups (Fig. 2). Although developed pressure

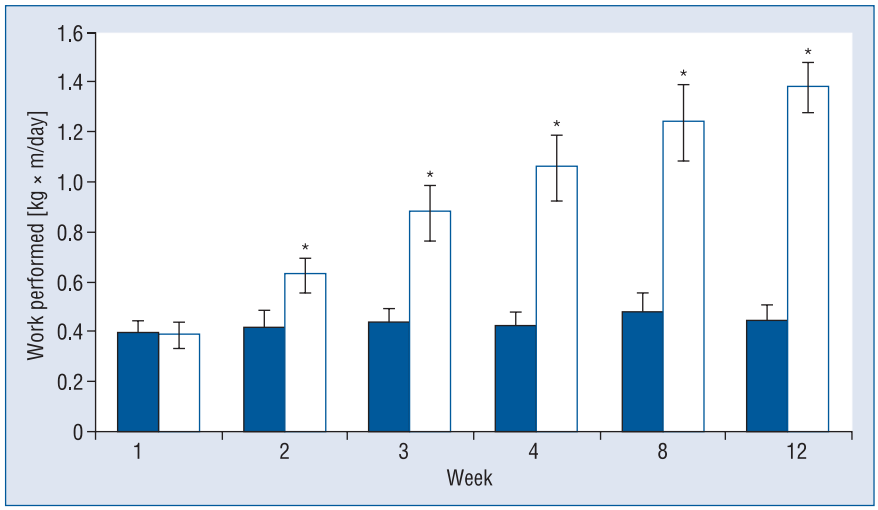


**Figure 1.** Work performed by rats during a period of resistance exercise training. Values are mean ± SD (n = 10 rats); *p < 0.01 compared to sedentary group; □ exercised and ■ sedentary rats.

and coronary flow decreased in trained and sedentary rats, both in ischemia and perfusion periods, there were differences between trained and sedentary groups in these parameters statistically.

After 35 min of ischemia, coronary flow and developed pressure were higher in trained than in untrained groups and this difference persisted until 50 min of reperfusion ($p < 0.01$). Also, the mean decrease in coronary flow and developed pressure were more significant during the protocol in the sedentary than in the trained animals ($p < 0.05$, Student's t test). The decline in developed pressure could be explained by diastolic pressure elevation (Fig. 2A). Moreover, diastolic pressure was significantly lower from 35 min of ischemia through 35 min of reperfusion in trained than sedentary rats ($p < 0.05$ for 35 min of reperfusion and $p < 0.01$ for other times).

## Infarct size

Figure 3 indicates the size of infarction in the hearts of trained and sedentary groups. Resistance exercise training reduced the infarct size statistically in trained rats compared to sedentary animals ($p < 0.05$).

# Discussion

## Weight-lifting ability and cardiac hypertrophy

The results of our study show that 12-week resistance exercise training induces an increase in weight-lifting ability and heart hypertrophy. These results are consistent with the findings of Barauna et al. [11], who reported that 12 weeks of resistance exercise induced an increase in weight-lifting ability and cardiac hypertrophy in rats. Increased weight-lifting ability indicates training efficacy and development. While maximum heart rate or maximal oxygen consumption are used to prescribe endurance exercise training [16], work performed may be a good indicator of resistance training efficacy. Moritany and deVries [17] showed that strength enhancement in response to training is a result of neuronal and muscular adaptations. Resistance training is a known stimulus for cardiac hypertrophy due to pressure overload imposed on the heart during training [18]. In this regard, our results agree with previous studies [11, 18]. It has been shown that resistance exercise-induced cardiac hypertrophy is accompanied by induction of the expression of angiotensin receptor type 1 [14] but the precise mechanism of cardiac hypertrophy in response to resistance training has yet to be determined.

## Cardiac preservation

Several studies have shown the beneficial effect of resistance exercise on cardiac performance in heart failure patients [8–10]. In this regard, it has been proposed that resistance training could improve stroke volume and ejection fraction without enhancement of cardiomegaly or cardiac deterioration [8–10]. But few studies have investigated the effect of this type of exercise on cardiac function in healthy individuals, and most of them did not show alteration of cardiac performance after resistance training [19–21]. Moreover, Barauna et al. [11] reported that 12 weeks of resistance training did not change cardiac function in the rats.

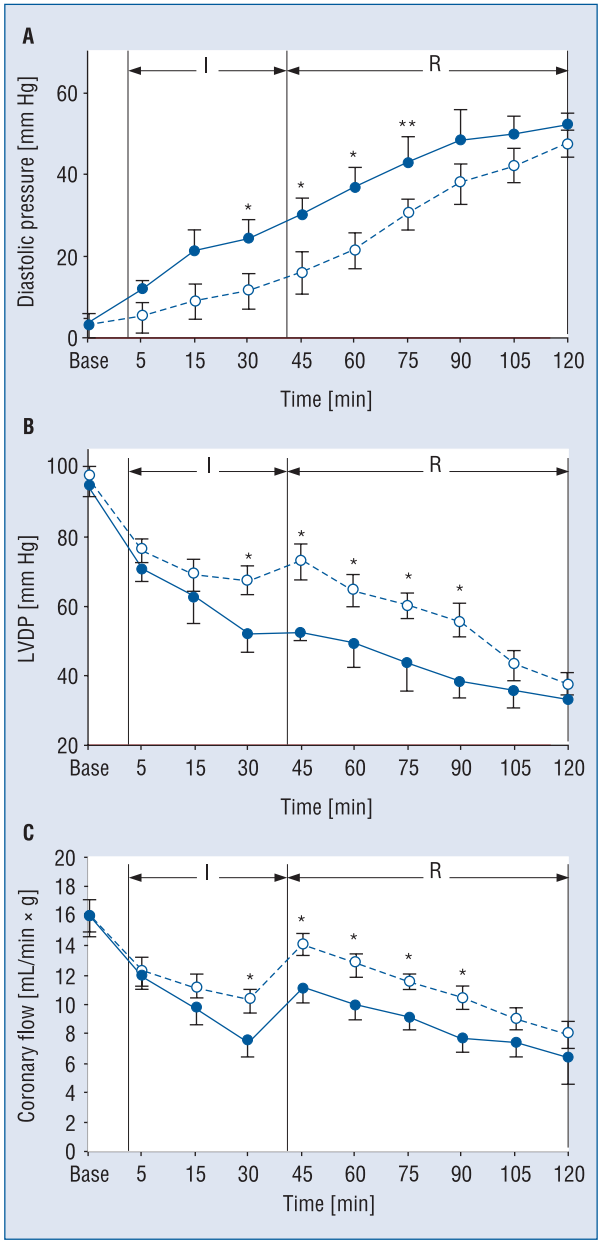


**Figure 2.** Hemodynamic indices of the heart during regional ischemia (I) and subsequent reperfusion (R); **A**. Diastolic pressure; **B**. Left ventricular developed pressure (LVDP); **C**. Coronary flow; values are mean ± SD (n = 10 rats); ○ exercised and ● sedentary rats; *, **: $p < 0.1$ and $p < 0.05$ as compared to the sedentary group respectively.

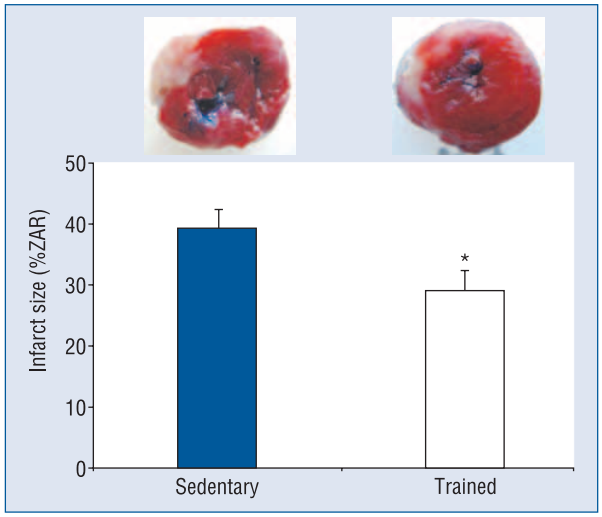


**Figure 3.** The effect of resistance exercise on the cardiac infarct size. **Top:** Representative digital images of stained heart. Non-necrotic viable tissue is red, and infarcted tissue is white. **Bottom:** Quantification of average infarct size expressed as percentage of ischemic zone at risk (ZAR); values are mean ± SD (n = 10 rats); *$p < 0.05$, significantly different from the sedentary group.

Our finding that 12-week resistance exercise elicited improved cardiac mechanical performance, coronary flow and myocardial infarction in the face of ischemia-reperfusion challenge is new and warrants discussion. Similar preservation by endurance training is a common finding and it has been reported by numerous investigations (see Powers et al. 2008 [1] for more details). Physiological mechanisms for endurance training-induced cardioprotection against ischemia-reperfusion injuries have not been precisely understood, but it has been proposed that some mechanisms such as alterations in coronary circulation, expression of endoplasmic reticulum stress proteins, increased cyclooxygnase-2 activity, induction of myocardial heat shock proteins, improved cardiac antioxidant capacity and elevation of ATP-sensitive potassium channels on both the sarcolemma and mitochondrial inner membranes may be involved in this cardioprotection [1, 15, 16]. Perhaps some of these mechanisms mediate the cardioprotective effects of resistance exercise against ischemia-reperfusion. In this regard, Chicco et al. [22] have reported that six-week resistance exercise protected against alcohol-induced myocardial stress by enhancing antioxidant defense. It is possible that alteration in coronary flow plays another role, as our results depicted better coronary flow as well as an improved hyperemic response in the beginning of the reperfusion period in trained hearts. Perhaps this phenomenon has contributed to improved left ventricular developed pressure. Nevertheless, this is the first study which investigates the effects of resistance exercise training on cardioprotection against ischemia-reperfusion-induced injury; precise conclusions will only come after further investigations.

## Conclusions

We have shown that long-term resistance training confers a cardioprotective effect against myocardial infarction in a defined region subjected to ischemia-reperfusion. The precise mechanism of this preservation is unclear, and the role of coronary flow and other possible mechanisms need more investigation.

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The authors do not report any conflict of interest regarding this work.

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