Hormozgan Medical Journal

doi 10.34172/hmj.2023.5119

Hormozgan Med J. 2023; 27(3): 140-145

Original Article

The Effect of High-Intensity Interval Training and Quercetin Nanoliposome Consumption on Angiogenesis Indexes in the Heart Tissue of Myocardial Infarction Rats

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Abstract

Background: Myocardial infarction (MI) is the death of the heart muscle tissue that causes damage and inflammation. Quercetin consumption and interval training can probably prevent the progression of this condition in the active parts of the myocardium by activating angiogenesis pathways and stimulating hypoxia factor-1a (HIF-1a) at the onset of infarction. This study investigated the effect of high-intensity interval training (HIIT) and quercetin nanoliposome consumption on angiogenesis indexes in the heart tissue of MI rats.

Methods: In this experimental study, 30 male rats weighing 250±20 grams were randomly divided into five groups: 1) MI+training, 2) MI+supplement, 3) MI+training+supplement, 4) healthy control, and 5) MI. MI was induced by subcutaneous injection of isoprenaline hydrochloride at a dose of 80 mg/kg. Groups 2 and 3 received quercetin daily at a dose of 0.25 mg/kg by gavage. Groups 1 and 3 performed five sessions of training protocol per week. Then, the Smirnov-Kolmogorov, one-way analysis of variance, and Tukey's post hoc test were used to analyze the data ($P<0.05$).

Results: Interval training and quercetin had a significant effect on increasing vascular endothelial growth factor (VEGF) and HIF-1a gene expression ($P<0.001$).

Conclusion: The combined effect of interval training and quercetin consumption may prevent the progression of MI by activating VEGF and HIF-1a in the early stages and play an effective role in preventing this disease.

Keywords: Training, Angiogenesis, Quercetin, Myocardial infarction

Received: October 18, 2021, **Accepted:** May 24, 2022, **Published Online:** September 28, 2023

Background

The World Health Organization (WHO) has reported myocardial infarction (MI) as the most common cause of heart failure. MI is pathologically referred to as myocardial cell death due to prolonged ischemia, which has the most severe symptoms of coronary artery disease (CAD). CAD causes the death of more than seven million people annually all over the world (1). Although cardiovascular diseases are costly for the health system, they are one of the most preventable non-communicable illnesses in humans (2). Researchers use a variety of processes such as angiogenesis to repair parts of the myocardium that have been inactivated. The development of angiogenesis leads to improving microcirculation through the formation of new capillaries and lateral artery vessels. As a result, the myocardium remains active in the early stages after MI, and the stage of long-term regeneration and heart failure occurs later (3). Vascular endothelial growth factor (VEGF) has been found to be one of the most important growth factors for the angiogenesis process, leading to increased permeability and the proliferation of endothelial cells (4). One of the major stimulators of angiogenesis is hypoxia. Tissues that are affected by hypoxia stimulate the hypoxia factor-1a (HIF-1a) (5). Previous studies have shown that hypoxia stimulates VEGF, so there is a critical relationship between hypoxia and angiogenesis (6). Supplements such as quercetin have a remarkable effect on the prevention and protection against cardiovascular disease. Quercetin, which belongs to a group of plant pigments called flavonoids, is found in numerous fruits and vegetables. The daily consumption of quercetin in the Western diet is about 15 mg, and this flavonol is found in onions and blueberries (7).

On the one hand, the number of people suffering from cardiovascular disease is increasing. On the other hand, clinical data suggest that acute inflammatory reactions after MI can accelerate the onset of general atherosclerosis, leading to the recurrence of MI. It seems necessary to control the inflammation caused by MI as soon as possible (8).

Studies have demonstrated that training has beneficial effects on cardiovascular disease depending on its mode, intensity, and duration. High-intensity interval training (HIIT) with high and low-intensity alternations is preferable to strength, endurance, and moderate-intensity training. Moreover, HIIT has an effective role

in improving exercise capacity, endothelial function, left ventricular thickness, and injection fraction (9). Following the effects of HIIT on signaling factors involved in vascular and molecular changes under myocardial ischemia, a study found that the levels of gene expression in HIF-1a, serine/threonine kinase (Akt), and VEGF were significantly different between the four groups, and HIF-1a in the ischemia group significantly increased compared to in other groups (10). Given the preference for interval training, a study compared the effectiveness of HIIT and endurance training on cardiac angiogenic factors and found that continuous endurance training increases endothelial nitric oxide synthase (eNOS), VEGF, and generally angiogenesis, whereas HIIT does not affect these factors (11). Another study reported that eight weeks of HIIT cause a significant increase in eNOS, VEGF, and other angiogenic factors (12).

Objectives

Despite the results of previous studies, the adaptations created by training and the response to release the resulting angiogenic stimuli under stress have not yet been identified. Moreover, no study has investigated the effect of HIIT with quercetin supplementation on VEGF and HIF-1a gene expression in the heart tissue of MI rats. Therefore, this study aimed to examine the effect of HIIT and quercetin nanoliposome consumption on angiogenesis indexes in the heart tissue of MI rats.

Methods

In this experimental study, 30 male rats with an approximate age of 6-8 weeks and weight of 250 ± 20 grams were purchased from the Pasteur Institute of Iran. Rats were kept at 23 ± 3°C with a humidity of 50 ± 10 and a light/darkness cycle of 12:12 hours. In addition, rats had ad libitum access to food and water until the end of the protocol. To create a model of cardiac ischemia, isoprenaline hydrochloride at a dose of 80 mg/kg (dissolved in 0.9% sodium chloride) was injected subcutaneously into 30 rats, and then they were randomly divided into five groups: 1) MI + training, 2) MI + supplement, 3) MI + training + supplement, 4) healthy control, and 5) MI.

To ensure the induction of MI, several rats in the MI groups were randomly anesthetized two days after MI. Their cardiac tissue samples were examined using the histochemical hematoxylin-eosin staining technique, then the eligible animals were participated in the research. All stages of keeping and killing rats were performed by the principles of the Animals' Ethical Committee of Islamic Azad University.

Investigation of Gene Expression

The concentration and purity of the extracted RNA were evaluated by a nanodrop spectrophotometer. The light absorption of the samples was measured at 260 and 280 nm, and its concentration was obtained based on the dilution coefficient in µL/ng. cDNA synthesis was performed using a cDNA synthesis kit,(Bio-Rad, Hercules, CA).

After measuring the optical density of the samples, the concentrations reached 1 ng / µL, and they were prepared for cDNA synthesis. Initially, 10 µL of Dnase1-treated RNA (1 ng / µL concentration) was poured into 0.2 microtubules, and 10µL of cDNA synthesis kit solution was added. Afterward, it was placed in a thermocycler for five minutes at 25 °C and then for 60 minutes at 60°C. The microtubules were cooled on ice and stored at -21 °C for qPCR, and primer design was performed using time-real PCR. The sequence of primers of forward-reverse genes is presented in Table 1.

Consumption of Quercetin Supplement with Liposome Nanoparticles

Quercetin supplement, which was converted into nanoparticles with liposomes, was administered by gavage daily at a dose of 0.25 mg/kg body weight. The first day of quercetin gavage was initially two days after adaptation to the training environment. During gavage treatment, quercetin nano liposomal supplementation was injected into two supplement groups at a dose of 10 mg/kg five days a week at a specific time (13).

Training Protocol

Rats in the training group performed the training protocol for eight weeks (five sessions per week), and the other groups were kept in laboratory condition during the implementation of the protocol. To implement the training protocol, rats in the training and training + supplementation groups were informed to work on the animal treadmill for two weeks. Then, to determine the intensity of exercise training, the maximum speed test was performed on the treadmill. After 10 to 20 minutes of warm-up at 40%-50% VO2 max intensity, the treadmill speed increased 0.03 m/s every two minutes until the animal was not able to run anymore. The speed at which blood lactate levels were above 6 mmol/L was considered the VO2 max speed.

According to Table 2, the main training protocol as HIIT was performed on an animal treadmill (Tajhiz Gostar,

Table 1. Sequence of Primers

Gene Name	Oligo Sequence
VEGF	F TGTGTGTGTGAGTGGCTT
	R ACCGAGAATACTGAAAAAAACCC
HIF-1a	F CAGGTGACCGTGCCCCTACTATG
	R CACAATCGTAACTGGTCAGCTGTG
GAPDH	F AGGTCGGTGTGAACGGATTTG
	R TGTAGACCATGTAGTTGAGGTCA

Note. VEGF: Vascular endothelial growth factor; HIF-1a: Hypoxia factor-1a; GAPDH: Glyceraldehyde 3-phosphate dehydrogenase.

Table 2. Aerobic Interval Training Protocol

No.	Week	Type of Activity	Speed (m/min)	Vo_{2max} (%)	Training Duration (min)	Repetition
1	1-8	Warm-up	10	50-55	10	7 (49 min)
		Interval training	25	80-90	4	
		Active rest between each training	15	65-75	3	
		Cool-down	5	20	5	

2016, Tehran, Iran) in the training group. It should be noted that no training shock was used during the training program, and if necessary, the animals were forced to continue training by using their hands or creating a sound stimulus on the cap of the treadmills (9).

Statistical Procedures

The Kolmogorov-Smirnov test was used to test the normal distribution of the findings. In addition, the one-way analysis of variance and Tukey's post hoc test ($P<0.05$) were used to analyze the hypotheses.

Results

Levels of HIF-1a and VEGF gene expression are presented in Figures 1 and 2, respectively. The one-way analysis of variance in HIF-1a ($F=5.738$, $P=0.0115$) and VEGF ($F=4.938$, $P=0.0185$) revealed a significant difference between different research groups.

Hypoxia Factor-1a Gene Expression

Regarding HIF-1a gene expression, the results of Tukey's post hoc test ($P<0.05$) showed that the effect of interval training and quercetin supplementation is significantly different in the control group compared to the MI group and in the MI group compared to the MI + supplementation + training group (Figure 1).

Vascular Endothelial Growth Factor Gene Expression

Regarding VEGF gene expression, the results of Tukey's post hoc test ($P<0.05$) indicated that the effect of interval training and quercetin supplementation is significantly different in the control group compared to the MI + supplementation + training group and in the MI group compared to the MI + supplementation + training group (Figure 2).

Discussion

The results of this study showed that eight weeks of interval training with quercetin supplementation significantly reduce the levels of HIF-1a and VEGF gene expression in the myocytes of rats with MI. In line with the results of the present study, Amlen et al found that exercise increases HIF-1α protein levels and increases further HIF-1α nuclear marking in skeletal muscle. In addition, HIF-1α activated the target gene VEGF, and

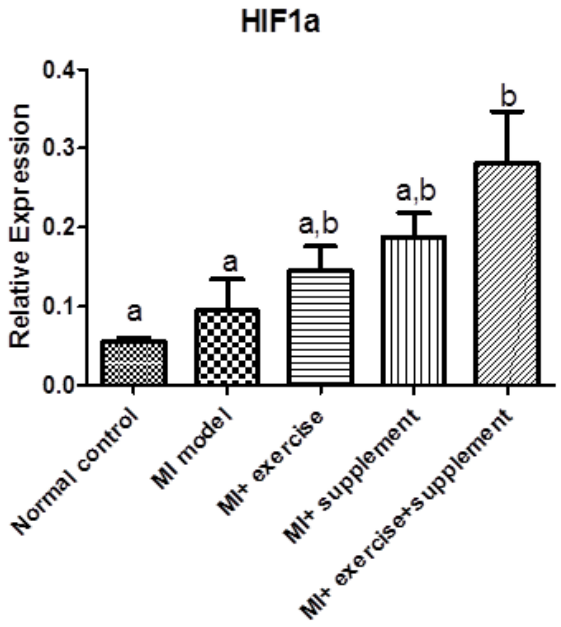

Figure 1. Changes in the Levels of HIF-1a Gene Expression in Different Research Groups. *Note.* HIF-1a: Hypoxia factor-1a. Dissimilar letters at the top of each bar show significant changes between different research groups ($P<0.05$). Similar letters at the top of each bar show a significant change ($P<0.05$)

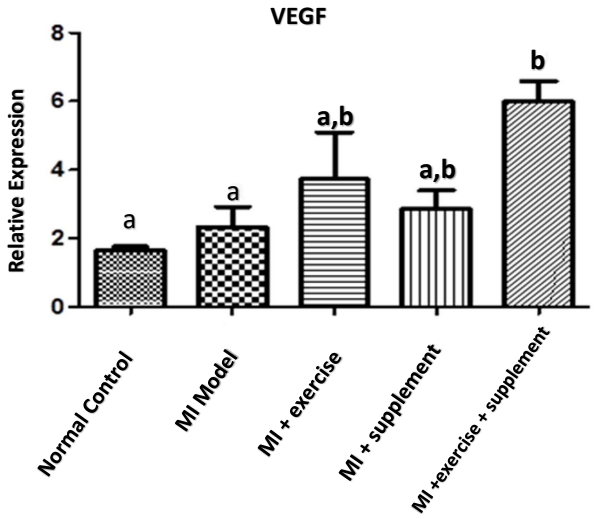

Figure 2. Changes in the Levels of VEGF Gene Expression in Different Research Groups. *Note.* VEGF: Vascular endothelial growth factor. Dissimilar letters at the top of each bar show significant changes between different research groups ($P<0.05$). Similar letters at the top of each bar show a significant change ($P<0.05$).
dehydrogenase

VEGF mRNA was increased by restricting blood flow to the athlete's foot (14). Furthermore, Zarezadehmehrizi et al studied the effect of eight weeks of aerobic training on VEGF and HIF-1a gene expression in the hippocampus of male rats and concluded that training causes a significant increase in these factors (15). In these studies, aerobic training was used, while no supplement was consumed, and the studied tissues were different. Moreover, Farhadi et al investigated the effect of aerobic exercises and interval hypoxia on the expression of angiogenesis-related proteins in the heart tissue of male Wistar rats. The results showed that phosphoinositide 3-kinases (PI3K)/Akt, VEGF, HIF-1α in the three groups of training, and hypoxia have a significant increase compared to the control group. Similar to the results of our study, hypoxia may be a better stimulus for the induction of angiogenesis, and aerobic training is more suitable for PI3K/Akt signaling pathway activity (16). Song et al examined the role and mechanism of HIF-1α and miR-126 in aerobic training-induced MI angiogenesis, which may generate new insights into the treatment of MI. The results revealed that four weeks of exercise training can significantly increase HIF-1α expression, while 2ME2 (HIF-1α inhibitor) partially reduced the therapeutic effect of exercise training. Results in living organisms displayed that HIF-1α can stimulate miR-126 expression in human umbilical vein endothelial cells in both normoxic and hypoxic states, and miR-126 or HIF-1a may be involved in the formation of human umbilical vein endothelial cell tubes under hypoxia via the PI3K/Akt/eNOS signaling pathway and Mitogen-activated protein kinase (MAPK) (17).

Inconsistent with the results of Lundby et al, some studies found that regular endurance training reduces HIF-1a and HIF-2a mRNA expression in human skeletal muscle under normoxic conditions. With hypoxic exposure, proteins HIF-1a and HIF-2a are stabilized. In contrast, HIF-1a and HIF-2 mRNA levels did not change at any point in time in the trained foot (18). Koltai et al showed an increase in HIF-1α levels after a six-week training program in older subjects, while these levels remained unchanged in younger subjects. They also asserted that regular exercise training reduces the difference between old and young rats regarding oxidative stress markers (19).

The main reasons for these differences were the type of training and the amount of applied intensity. Moreover, no supplement was taken. Most importantly, the studied target tissue was different. It can be concluded that the expression of these genes in different tissues may not have the same responses to different types of exercise training. Exercise training has been shown to improve endothelial function through vasodilation and improving vasomotor function. The formation of new capillaries and ultimately the increase in capillary density are the most important changes that occur during exercise, and this ultimately leads to an increased and augmented delivery of oxygen to the muscle fibers (20).

Exercise training following MI reduces the area of infarction and increases capillary density (21). During exercise, reactive oxygen species increase, and this consequently activates AMP-activated protein kinase (AMPK) and P38MAPK and results in an increase in VEGF and activation of the angiogenesis process.

Another factor affecting signaling pathways of angiogenesis is mechanical forces. During exercise training, muscle contractions increase, leading to increased muscle tension and eventually increasing muscle blood flow by about 20 times normal conditions. Furthermore, muscle tension increases, endothelial cells become more stretched, and blood flow and vascular production increase. These forces increase the release of calcium ions, and calcium ions activate eNOS (22). Regarding the effectiveness of quercetin, Shasha et al suggested that quercetin can reduce heart damage from high-fat diets in rats by restoring a small loop of systemic circulations. Some rats were fed with standardized food for six months and treated with quercetin supplementation for an additional 10 weeks (23). The results indicated that quercetin may directly induce angiogenesis and reduce myocardial oxidative stress.

Quercetin induces phosphorylation of the eNOS, thereby it leads to an increase in nitric oxide (NO) release, improves cardiac blood flow, and paves the way for angiogenetic processes (24). Quercetin contributes to vascular health with its antioxidant effects, thereby increasing the transfer of oxygen and nutrients from the blood to the muscles, joints, and tissues involved during exercise.

Exercise and MI are both conditions that reduce access to blood oxygen levels and provide the stimuli for the release of HIF-1a, which is an oxygen-sensitive factor. The pathways that produce active HIF levels in the cell are the PI3K/Akt, mammalian target of rapamycin (mTOR), and the mitogen-activated protein kinase pathways, which converge on p70S6 and 4E-eIF kinase-binding proteins and increase the translation of HIF-1a mRNAs (25). On the other hand, VEGF gene expression depends on several factors such as hormones, growth factors, and oxygen concentration. HIF-1a also increases VEGF gene expression due to hypoxic conditions (15). Iemitsu et al suggested that physical activity increases VEGF gene expression in the myocardium, which is accomplished by the kinase pathway and protein B kinase, also known as Akt. Akt leads to an increase in eNOS levels (26). In the early stages of angiogenesis, the up-regulation of VEGF depends on the release of NO. During exercise, NO release is increased during contraction in response to high blood flow or shear stress by vascular endothelium and muscle fibers (12).

One of the limitations of this study was not measuring

AMPK and mTOR protein levels; furthermore, it did not consider different training intensities. To confirm the findings of this study, it is recommended that future studies should evaluate the effects of interval training at different intensities together with the measurement of AMPK and mTOR protein levels in the myocardial tissue of rats with MI.

Conclusion

The results of this study indicated that in the hypoxic conditions in rats, the concurrent effect of HIIT and quercetin supplementation compared to the effect of either one alone may increase VEGF and HIF-1a gene expression at the onset of infarction by stimulating the mTOR pathway, inhibiting inflammatory reactions, and reducing further development of cell death. It appears that quercetin supplementation plays a role in the progression of MI through the PI3K/Akt/eNOS and MAPK signaling pathways and activates the stimuli needed to inhibit the angiogenesis process.

Acknowledgments

This research is extracted from a Ph.D. dissertation in Cardiovascular and Respiratory Physiology. In this vein, the authors would like to express their sincere gratitude to the esteemed officials of Khorasgan University.

Authors' Contribution

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Competing Interests

The authors declare no conflict of interests.

Ethical Approval

The research was approved by the Ethics Committee of the Islamic Azad University with the code IR. IAU. KHUISF. REC.1400.092.

Funding

No one funds this study.

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