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Responses of some matrix metalloproteinases activities to an acute session of endurance exercise and electrical stimulation in induced myocardial infarction in Wistar rats

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Abstract. – OBJECTIVE: Myocardial infarction is the irreversible cell death of cardiac muscle that takes place after the blood flow is cut off to a specific region of the heart muscle. The molecular angiogenesis process that may follow after the incidence, due to any activity or its intensity, is unknown. The purpose of this research was to examine some of the matrix metalloproteinase (MMP) responses to an acute course of endurance exercise and electrical stimulation in induced myocardial infarcted Wistar rats.

MATERIALS AND METHODS: In this experimental case-control study, 40 induced myocardial infarcted Wistar rats (8-week-old, mean weight 130±30 g) were randomly assigned into 4 conditions: endurance exercise, exercise + electrical stimulation, only electrical stimulation, and control group. The infarction was induced 24 hours after the subcutaneous injection of 150 mg/kg of Isoproterenol. The exercise and exercise plus electrical stimulation groups performed a session of endurance exercise on an animal treadmill, at 20 m/min for one hour. The electrical stimulation was delivered by foot shock, set with the intensities of 0.5 mA for 20 minutes. Immediately after the cessation of the treatment protocol, MMP1, MMP2, and MMP9 were measured by the ELISA method. Data analysis was performed by using Two-way ANOVA and significance was set at α = 0.05.

RESULTS: One session of endurance exercise or electric stimulation, or their combination, had no significant effect on the level of MMPs.

CONCLUSIONS: One session of acute endurance exercise, stimulation, or their combination, elicited no significant effect on the level of MMPs of artificially induced myocardial infarcted Wistar rats.

Key Words:
Myocardial infarction, Matrix metalloproteinase, Endurance exercise, Electrical stimulation.

Introduction

Cardiovascular disease is the leading cause of morbidity and mortality in the world, responsible for approximately 17.9 million deaths globally[1]. Myocardial infarction (MI) is the most known cause of these diseases[2], and it is anticipated that, by the year 2030, nearly 23.6 million people will lose their life for this reason[3]. One of the adaptations that may follow after a MI is angiogenesis

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which is the process in which endothelium cell growth and arteries are activated, and new blood vessels are formed[4,5]. Considering that 70% of MI incidences occur due to atherosclerosis (AS)[6], the balance between the angiogenic and angiostatic processes is important for rehabilitation after ischemia[7]. Angiogenesis is a natural event in reaction to myocardial hypoxia and it takes place in the absence of hypoxia. The decrease in oxygen partial pressure due to exercise is one of the most important causes of angiogenesis[8]. The increase in hypoxia-inducible factor 1-alpha (HIF-1a) and vascular endothelial growth factor (VEGF) protein, following the adaptation to exercise, has been confirmed, and angiogenesis has been demonstrated[9]. The angiogenesis factors, by attaching to their receptors, activate endothelium. Accordingly, following endothelial cell activation, different types of metalloproteinases are secreted from targeted cells that, in turn, lead to basement membrane disintegration. As the dissolving of the basement membrane begins, the environment for the proliferation and migration of the endothelial cell starts. Consequently, pericytes and the cells of smooth muscle, for the consolidation of new blood vessels, are added to the formation site[10]. One of the effective factors in the initiation of angiogenesis is the activation of matrix metalloproteinases (MMPs)[7]. These MMPs are a member of endogenous enzymes that are collagenase mediators; they are zinc and calcium-dependent[11] and cause degradation of extracellular matrix (ECM) proteins. Kaminski et al[12] reported that they are very active during MI and are implicated in rebuilding ECM in several physiological and pathological processes. MMPs are believed to form more than 20 distinctive proteins[11], and the majority of these enzymes, which are inactive, become activated in ECM. Indeed, they not only break the ECM, but also act as a signal mediator of cytokines during the physiological activities of leukocyte cells[12]. Some reports[12,13] suggest that MMP-1 gelatinase MMP-2 and MMP-9 have a more advanced role in rebuilding myocardial and collagenase.

In addition to the treatment of MI patients, there are other methods in complementary medicine for treating cardiovascular problems. Indeed, participation in exercise programs is the first line of prevention, as well as rehabilitation[14]. Xu et al[15] reported that, in infarcted Wistar rats that performed exercise, a higher ratio of MMP-1/tissue inhibitor of metalloproteinase-1 (TIMP-1) was found compared to non-exercised rats[15]. Danzing et al[16] demonstrated that MMP2 did not change in response to exercise, whereas MMP9 showed an acute increase following participation in an exercise program[16]. Koskeen et al[17] also showed an acute increase of MMP2 following the participation in exercise[17]. In addition to exercise, electrical stimulation (ES) is regarded as a new and effective rehabilitation measure to treat ischemia[18]. Considering the extant research, it is expected that ES may serve as an effective rehabilitative measure for individuals who take part in exercise programs[19].

There is a paucity of research in which MMPs have been examined following participation in physical activities and electrical stimulation after infarction. The topic of MMPs and their response to exercise and electrical stimulation is novel and there are no unanimous views in the literature. However, even though the positive effect of exercise and electrical stimulation on different aspects of heart health in myocardial infarcted patients has been studied[14,18], the physiological mechanism and inflammatory factors involved are not well understood. Thus, this research sought to examine the matrix metalloproteinase response in Wistar rats under an induced myocardial infarction to an acute course of endurance exercise combined with electrical stimulation.

Materials and Methods

Animal Selection

For the purpose of this research, 40, 8-week-old, male, Wistar rats, with a mean weight of 130±30 g, were purchased from the Pasteur Institute of Iran. The animals were kept in clear polycarbonate cages, at a controlled temperature of 22±2 degrees centigrade, at a humidity level of 50±5 percent, and a dark-light cycle of 12:12, with free access to water and Wistar special food. After the animals were transferred to the exercise environment, they were kept for one week for adaptation to the new environment. Next, they were randomly assigned into 4 equal groups (n=10) of endurance exercise (MI.EX), only electric stimulation (MI.ES), endurance exercise + electric stimulation (MI.EX.ES), and control group (MI).

Experimental Procedure

Myocardial infarction was induced by subcutaneous injection of Isoproterenol (Sigma Chemical Co., St. Louis, MO, USA) at 150 mg/kg of body weight[20]. Isoproterenol was mixed with 0.05 cc of normal saline to dilute it and was injected in two consecutive doses at 24-hour intervals. This is a

Table I. Descriptive statistics for the MMP1 based on stimulation and exercise conditions.

Stimulation	Exercise	Mean	Std. Deviation	N
Stimulation	Stimulation	3.60	0.89	7
	Exercise	2.95	0.90	7
	Total	3.27	0.93	14
Exercise	Stimulation	3.38	0.63	7
	Exercise	2.95	1.24	7
	Total	3.17	0.97	14
Total	Stimulation	3.49	0.75	14
	Exercise	2.95	1.04	14
	Total	3.22	0.93	28

routine procedure for inducing myocardial infarction in Wistar rats[21]. After 48 hours post-injection, some rats were randomly selected and examined for the myocardial infarcted condition to assure the presence of MI in all groups. The MI condition was confirmed based on the electrocardiograph changes (ST-elevation segment) and simultaneous increase of cardiac troponin I (344/01 pg/ml).

R12 Electromodule set (Sciencebeam Co., Tehran, Iran) was employed to deliver electrical stimulation. The intensity of electrical stimulation was 0.5 mA for 20 minutes that was sent through the output stimulator, regulated as Trial Number: 1, Trial Period: 1200000, Recording Time: 1200000 sent to foot stimulation set[22-24]. The treadmill familiarization stage included one week of training according to standard protocols[24]. The rats were conditioned through voice and stimulation in order to avoid resting and contacting with the electric stimulation section located at the end of this set. The endurance exercise program included running on a treadmill, set to zero elevation, for one hour at 60 percent of their maximum oxygen consumption[25], at a speed of 20 m/sec. After the end of the training protocol, the animals were sedated by a compound of ketamine (75 mg/kg) and Xylazine (10 mg/kg), and humanely slaughtered.

Blood samples were directly drawn from the right ventricle after the sedation by tubed syringe and decanted into a clot gelled tube. Blood was then centrifuged for 5 minutes at a speed of 5000 rotations per minute (RPM); then, all the collected serum samples were kept at -80°C for chemical analysis. For assessing the level of MMP1, MMP2, and MMP9 in the lab, the ELISA method, according to the kit manufacturer instructions made by Hangzhou Eastbiofarm Co. Ltd (Hangzhou, China) (with a variation coefficient of less than 10% for every kit and sensitivity of 0.05, 0.01 and 0.028 ng/ml), was used.

The Ethical Approval to conduct the study was issued by Islamic Azad University of Arak (IR.IAU.ARAK.REC.1398.011).

Statistical Analysis

Mean and standard deviation (SD) values were calculated for each variable. After the normality of data distribution was confirmed by Shapiro-Wilk test, parametric statistics, including Two-way analysis of variance (ANOVA), was used to analyze the data using SPSS (version 20, IBM Corp., Armonk, NY, USA). Statistical significance was accepted, *a priori*, at $p<0.05$.

Results

MMP1 Based on Stimulation and Exercise Conditions

Descriptive statistics for serum MMP1 levels, according to exercise and stimulation conditions, are presented in Table I and graphically shown in Figure 1. The results of Two-way ANOVA showed

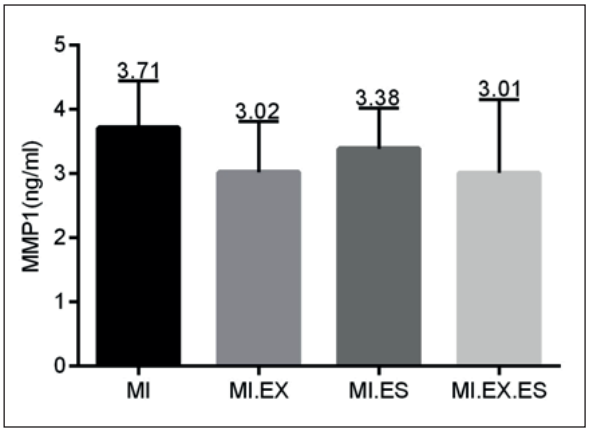

Figure 1. Serum levels of MMP1 for MI, MI.EX, MI.ES and MI.EX.ES groups.

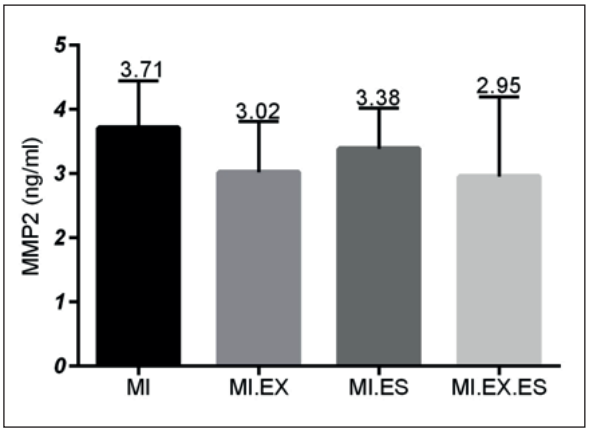

Figure 2. Serum levels of MMP2 for MI, MI.EX, MI.ES and MI.EX.ES groups.

that there was no main effect for the stimulation or exercise condition, and there was no significant interaction effect between these variables (p=0.768, p=0.142, and p=0.762, respectively). These results are presented in Table I.

MMP2 Based on Stimulation and Exercise Conditions

Descriptive statistic for serum MMP2 level according to exercise and stimulation condition is presented in Table II and graphically shown in Figure 2. The result of two-way ANOVA also showed no main effect for the stimulation or exercise condition and there was no significant interaction effect between these variables (p=0.658 p=0.134, and p=0.308).

MMP9 Based on Stimulation and Exercise Condition

Descriptive statistics for serum MMP9 levels based on exercise and stimulation conditions are presented in Table III and graphically shown in Figure 3. The result of two-way ANOVA also showed no main effect for the stimulation or exercise conditions. There was also no significant interaction between these variables (p=0.658, p=0.134, and p=0.308).

Discussion

Myocardial infarction is a cardiovascular incident that results in cardiac ischemia and malfunction of the heart muscle, leading to pathological cardiac hypertrophy and decrease of capillary density. The decrease of capillary density increases the risk of cardiac muscle cell death[26]. Thus, the re-angiogenesis in cardiac tissue improves cardiac output and the amount of blood pumped by the heart and left ventricular ejection fraction, which consequently enhances the cardiovascular function of patients. For this reason, examining the factors involved in angiogenesis and angiostatic helps identifying the effective methods to increase angiogenesis and improve the health quality of the cardiac patient[27]. Matrix metalloproteinases play an important role in the process of angiogenesis[28]; they are necessary for the migration of the endothelial cells if the ECM and base membrane are to dissolve. Moreover, the intercellular connection also needs to be disintegrated. The purpose of this research was to examine the changes in the serum level of MMP1, MMP2, and MMP9, after taking part in an endurance exercise program, in addition to receiving an electric stimulation, in Wistar rats with induced MI. Our results showed that participation in an endurance exercise program did not significantly change the level of MMP1, MMP2, and MMP9 in the induced myocardial infarction Wistar rats. In addition, the results showed that the endurance exercise program combined with an electric stimulation delivery to these animals elic-

Table II. Descriptive statistics for the MMP2 based on stimulation and exercise conditions.

Stimulation	Exercise	Mean	Std. Deviation	N
Stimulation	Stimulation	11.15	2.31	7
	Exercise	9.10	2.63	7
	Total	10.13	2.60	14
Exercise	Stimulation	10.68	1.92	7
	Exercise	10.28	1.24	7
	Total	10.48	1.57	14
Total	Stimulation	10.92	2.059	14
	Exercise	9.69	2.069	14
	Total	10.30	2.120	28

Table III. Descriptive statistics for the MMP9 based on stimulation and exercise condition.

Stimulation	Exercise	Mean	Std. Deviation	N
Stimulation	Stimulation	1.71	0.18	7
	Exercise	1.52	0.52	7
	Total	1.62	0.39	14
Exercise	Stimulation	1.71	0.45	7
	Exercise	1.53	0.17	7
	Total	1.62	0.34	14
Total	Stimulation	1.71	0.33	14
	Exercise	1.53	0.37	14
	Total	1.62	0.36	28

ited no significant changes in the level of MMP1, MMP2, and MMP9. The unchanged MMP1 level observed in the present study was discordant with the findings of Melek et al[29], who showed a decrease in MMP1 levels, and those of Urso et al[30] who showed an increase in MMP1 level of induced MI Wistar rats[30]. The contradictory findings could be explained by the difference in the methodology employed in the different studies.

The second finding of the present research was the non-significant decrease of MMP2 in the Wistar rats under the induced MI condition. This finding was concordant with the results of some other investigators[17,31]. However, these research findings contradicted the findings of Koskinen et al[31], who demonstrated that the level of MMP2 increased after one session of exhaustive exercise in Wistar rats. Tayebjee et al[32] also reported an increase in the level of MMP2 after a session of endurance exercise in Wistar rats, which was similar to the findings of Suhr et al[33]. Our results, regarding the level MMP9, were similar to the findings of MMP1 and MMP2: no significant change was found after the endurance exercise and stimulation, alone or combined, even though a decrease was observed. Indeed, such findings were similar to a previous research report[34] wherewith coronary heart disease diseases participated in an endurance exercise program. On the contrary, the results of some other research do not support the findings of the present research regarding the changes in the level of MMP9 in response to endurance training programs[31,35,36]. The reason for these controversial findings may be attributed to the difference in types of endurance training, participants, or sampling methods[30]. For instance, the program used in Tayebjee et al[32] was the Bruce protocol, which includes six stages of three minutes activity in which in every stage the intensity is changed by increasing the elevation and speed of the treadmill up to the point of exhaustion. Thus, the observed study differences may be due to the greater damage to more muscle myofibrils involved in the activity during the uphill running, leading to more changes in serum level of MMPs[32], as compared to the endurance exercise protocol employed in the present research, which was performed at moderate intensity. Another reason for such discrepant findings may be due to the use of high intervals and persistent training frequency[33]. In addition, it has been shown that the changes in MMPs are dependent on the intensity. Indeed, exercise protocols performed at above 70% of oxygen consumption can elicit an increase in the level of MMPs, whereas programs performed at 50% of maximum oxygen consumption do not lead to such changes in MMPs[37]. A further reason for observing such differences may be attributed to the activation of enzymes involved in the microanatomy structure of cardiac and skeletal muscles[38] since myocardial infarction was induced in the samples used in the present research. The other findings of the present study were the insignificant decrease in serum levels of MMP1, MMP2, and MMP9 in response to ES, and a combination of acute endurance training

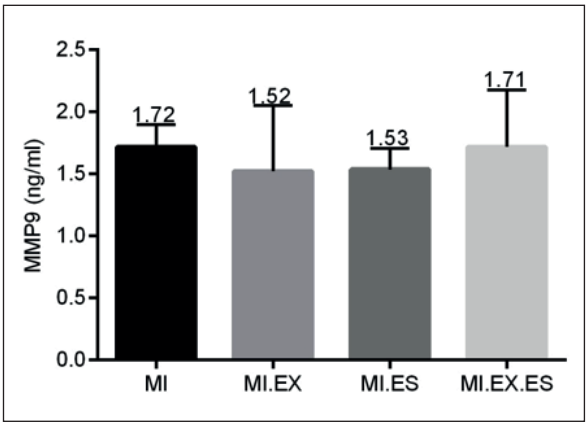

Figure 3. Serum levels of MMP9 for MI, MI.EX, MI.ES and MI.EX.ES groups.

and ES, in all study groups. However, in reviewing the extant literature in this regard, no comparable findings were found, which clearly highlights that further elucidation is required.

Conclusions

One session of endurance exercise, alone or combined with electric stimulation, did not change the level of matrix metalloproteinases, including, MMP1, MMP2, and MMP9, in Wistar rats with induced myocardial infarction. More research is needed to identify treatment regimens that improve angiogenesis post-myocardial infarction.

Ethical Considerations

The study was approved by the Islamic Azad University of Arak (Number: IR.IAU.ARAK.REC.1398.011).

Conflict of Interest

The authors declare no competing interests.

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