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The Effect of One Bout Submaximal Endurance Exercise on the Innate and Adaptive Immune Responses of Hypertensive Patients

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Abstract

Introduction: Changes in some of the immune system factors are associated with a risk of cardiovascular disease. Therefore, the purpose of this study was to investigate the effect of one bout sub-maximal endurance exercise (OBSEE) on the innate and adaptive responses of hypertensive patients.

Methods: From among 70 men with hypertension, 20 men (Mean ± SD, age: 60.25 ± 4.59 yrs, body mass index (BMI): 29.57 ± 3.68 k/m^2, and the maximal oxygen uptake (Vo_{2max}): 34.83 ± 2.11 ml/kg/min) were chosen. The statistical sample performed OBSEE for 30 minutes at 60-65% of the maximum heart rate reserve (MHRR). Blood sampling was performed to measure the response of immunoglobulin A (IgA), immunoglobulin G (IgG), immunoglobulin M (IgM), white blood cells (WBC), neutrophils (NEUT), basophils (BASO), eosinophils (EO), monocytes (MONO) and lymphocytes (LYMPH) of hypertensive patients before and immediately after exercise. Shapiro-Wilk test was used to normalize the research data. To analyze the data, paired sample t-test was used at significant level ($P \leq 0.05$). The hypothesis test was performed using SPSS software version 19.

Results: Sub-maximal endurance exercise significantly increased IgA ($P = 0.001$), IgG ($P = 0.001$), IgM ($P = 0.001$) and WBC ($P = 0.001$) in hypertensive patients. On the other hand, a significant decrease in EO levels ($P = 0.001$) was observed after OBSEE. Significant changes were not found in NEUT ($P = 0.907$), BASO ($P = 0.383$), MONO ($P = 0.220$) and LYMPH ($P = 0.422$) levels.

Conclusion: It seems that OBSEE can reduce the risk of cardiovascular disease caused by elevated EO in these patients, while enhancing the adaptive immune system in hypertensive patients.

Keywords: Exercise, Innate Immunity, Adaptive Immunity, Hypertension

Introduction

Hypertension is considered to be the main risk factor for cardiovascular disease in adults and reduces life expectancy by seven years (1).The exact mechanism that leads to hypertension is still unknown. Recent evidence suggests that circulating inflammatory cytokines may lead to the development and maintenance of high blood pressure (2, 3). Inflammation plays a major role in high blood pressure (4). In addition, several studies which provided results on the presence of macrophages and T cells in the kidneys and vascular system of hypertensive individuals (5, 6) have shown that the immune system directly plays a role in the pathogenesis of hypertension (2). Leukocytes, called white blood cells (WBC), are motor units of the body's defense system. The total white blood cell count of an adult is about 7,000 cells per microliter of blood. Of these, 62% are of neutrophils (NEUT), 0.4 % of basophils (BASO), 3.2% of eosinophils (EO), 5.3% of monocytes (MONO) and 30% of lymphocytes(LYMPH). Of the WBCs, B and T lymphocytes are two main arms that are considered as adaptive immunity. The function of other WBCs is known as innate immunity. Lymphocyte B plays a role in the production and secretion of immunoglobulins (7).

Immunoglobulins are a heterogeneous group of immune system proteins that consist of four polypeptide chains (two light chains and two heavy chains). It has been shown that there is a relationship between immunoglobulin G (IgG), immunoglobulin A (IgA), immunoglobulin M (IgM) and hypertension (8). Wang *et al*. (2018) showed that decreased IgM and increased IgG and IgA were associated with a high prevalence of hypertension (8). IgA is the main class of antibodies in the body seen in saliva, tears and intestinal mucosa (9- 11). This antibody is the first defense line of the body against upper respiratory tract infection (URTI) that reducing its levels increases the risk of URTI (12, 13). The position of IgA is higher in serum, gastric mucosa, respiratory tract, genitalia and milk. This secretory antibody represents the immune system, which is responsible for maintaining homeostasis at mucosal surfaces. The baby receives the first group of this antibody in the form of IgA secreted antibody through breast milk. This process continues as long as the child's immune system can produce it (14).

Immunoglobulin G is the chief type in the blood, which appears during primary and secondary immune responses through the activation of complementary systems and macrophages. This immunoglobulin is the only class of antibodies that can cross the placenta and provide baby's immunity.

Immunoglobulin M is the largest antibody in the blood circulation system, which is exposed as the first antibody to the antigen (9- 11). Studies show that the adaptive immune system may change through physical activity (15). Mackune *et al*. (2005) reported an increase in IgA, IgG and IgM levels immediately after ultra marathon running (16). It has also been shown that conducting one bout submaximal endurance exercise (OBSEE) of 30 to 45 minutes in hypertensive patients reduces systolic blood pressure by 30 to 40 mmHg and diastolic blood pressure by 15 to 20 mmHg (17). Since less research has investigated the relationship between hypertension and adaptive and innate immune system factors, this study attempts to investigate the effect of OBSEE on IgA, IgG, IgM, WBCs, LYMPH, MONO, NEUT, BASO and EO in patients with hypertension.

Methods

Considering the purpose, the present research is applied, which is performed in a semi-experimental way with a pre-test post-test research design. Therefore, in the current study, the effect of OBSEE on the innate and adaptive immune responses of hypertensive patients was studied. The protocol and methods of this study were approved by the Islamic Azad University of Omidieh Branch. The sample comprised 20 men of 55 to 65 years who were working in the National Iranian South Oil Company (NISOC). The subjects were suffering from high blood pressure, which were selected from among 70 individuals based on inclusion and exclusion criteria. The criteria for inclusion and selection of subjects included: 1. The age range of 55 to 65 yrs; 2. The Vo_{2max}> 7.5 METs; 3. systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg. Exclusion criteria included: 1. The age range below 55 or above 65 yrs; 2. The Vo_{2max}< 7.5 METs; 3. systolic blood pressure < 140mm Hg or diastolic blood pressure < 90 mm Hg; 4. Smoking; 5. Other illnesses including coronary artery disease and diabetes. To evaluate the cardiovascular endurance of the subjects, a modified Bruce test was used. Resting systolic and diastolic blood pressure was also determined using digital pressure gauge. After selecting samples and one-week interval, the groups underwent OBSEE for 30 minutes with a 60- 65 % maximal heart rate reserve (MHRR), following an 8-hour fasting protocol (18). In order to prevent the effect of the activities prior to testing on innate and adaptive immune responses, all subjects were requested not to participate in any intensive activity 48 hours prior to the protocol of OBSEE (18, 19).

Blood samples were taken before and immediately after the exercise to examine IgA, IgG, IgM, WBCs, LYMPH, MONO, NEUT, BASO and EO responses in patients with high blood pressure. In order to evaluate the complete blood count (CBC), two milliliters of blood from brachial intravenous vein was taken in tubes containing EDTA with concentrations of one and a half to two milligrams per milliliter. Also, five milliliters of blood were transferred to the clot tube. Blood sample in the clot tube was centrifuged for serum isolation and for measuring immunoglobulins and other factors for 15 minutes at a rate of 3000 rpm. Shapiro Wilk test was used to normalize the research data. Also, to assess the innate and adaptive immune responses in hypertensive patients with hypertension after the endurance exercise, paired sample t-test was used with significant level ($P \leq 0.05$). To test the research hypotheses SPSS software version 19 was employed.

Results

Table 1 shows the descriptive information on the anthropometric and physiological indices of the sample. The results of Table 2 show the information on the paired sample t-test of the research variables. The results of this table show that OBSEE significantly increased the levels of IgA (P = 0.001), IgG (P = 0.001), IgM (P = 0.001), WBC (P = 0.001) and significantly decreased the level of EO (P = 0.001) in patients with hypertension. Significant changes were not observed in the levels of NEUT (P = 0.907), BASO (P = 0.383), MONO (P = 0.220), and LYMPH (P = 0.422) in hypertensive patients after OBSEE. Table 3 shows the results of the correlation between the variables. Considering the significant level (P = 0.005) and correlation coefficient (R = +0.60), it can be stated that there is a significant positive correlation between SBP and EO. Also, the correlation between Vo_{2max} and IgG is positive (P = +0.44) and significant (P = 0.049). On the other hand, there is a significant correlation between Vo_{2max} and SBP (R = -0.73) (P = 0.001). In addition, there is a significant negative correlation between Vo_{2max} and EO (R = -0.53) (P = 0.016).

Discussion

The results of this study showed a significant negative correlation coefficient between Vo_{2max} with SBP (R = -0.73) and EO (R = -0.53). On the other hand, there was a significant positive correlation between SBP and EO (R = +0.60). For the past thirty years, Vo_{2max} has been a major predictor of cardiovascular disease and mortality. Evidence suggests that exercise will improve Vo_{2max} levels, so that increase in each MET in Vo_{2max} is associated with 10 to 25 percent improvement in longevity. Therefore, increasing Vo_{2max} can reduce the risk of cardiovascular disease (20). The results of this research also confirm this point. In the present study, the increase in Vo_{2max} levels was associated with a decrease in SBP and EO. Both increases in SBP and EO will increase the risk of atherosclerosis (21) Therefore, any increase in Vo_{2max} can improve cardiovascular health. One of the most controversial results of this research is the positive and significant relationship between Vo_{2max} and IgG. IgG is the main immunoglobulin in the blood, which appears during primary and secondary immune responses by activating complementary systems and macrophages (9- 11). Therefore, an increase in Vo_{2max} levels has been associated with improvements in immune response. The results of this study showed that OBSEE resulted in a significant increase in the levels of IgA, IgG and IgM in hypertensive patients. Among immunoglobulins, IgA is the first defense line of the body against URTI (12) and reducing it increases the risk of URTI (13). This secretory antibody represents the immune system, which is responsible for maintaining homeostasis at mucosal surfaces (14).

Table 1. Descriptive data on the anthropometric and physiological characteristics of the subjects

Variable	M±SD
Age (yrs)	60.25±4.59
Height (cm)	6.34±171.10
Weight (kg)	12.33±86.70
Body Fat Percentage (BFP) (%)	3.18±23.00
Vo_{2max} (ml/kg/min)	2.11 ±34.83
Systolic Blood Pressure (SBP) (mm Hg)	6.43±147.20
Diastolic Blood Pressure (DBP) (mm Hg)	3.70±94.40
Resting Heart Rate (RHR) (beat/min)	3.61±76.25

Table 2. Paired sample t-test results

Variable	Number	Pretest M±SD	Posttest M±SD	Changes (%)	t	Sig
IgA (g/L)	20	2.51±0.98	2.75±1.14	+ 9.56	-3.865	0.001•
IgG (g/L)	20	10.54±1.81	11.54±1.90	+ 9.48	-5.354	0.001•
IgM (g/L)	20	0.74±0.31	0.82±0.33	+ 10.81	-5.076	0.001•
WBC (10^3/uL)	20	7.48±0.59	9.37±0.61	+ 25.26	-7.030	0.001•
NEUT (%)	20	53.11±9.52	52.90±9.37	- 0.39	+0.119	0.907✪
EO (%)	20	2.59±1.39	1.94±1.12	- 25.09	+5.520	0.001•
BASO (%)	20	0.39±0.14	0.37±0.12	- 5.12	0.893	0.383✪
MONO (%)	20	7.82±1.20	7.61±1.39	- 2.68	+1.269	0.220✪
LYMPH (%)	20	35.06±7.96	36.40±8.71	+ 3.82	-0.821	0.422✪

M±SD: mean±standard deviation, IgA: immunoglobulin A, IgG: immunoglobulin G, IgM: immunoglobulin M, WBC: white blood cells, NEUT: neutrophil, EO: eosinophil, BASO: basophil, MONO: monocyte, mean, LYMPH: lymphocyte, • significant changes, ✪ no significant changes.

Table 3. Results of Pearson Correlation Coefficient

First Variable	Second Variable	R	R^2	Sig
SBP (mm Hg)	EO (%)	+0.60	0.36	0.005•
Vo_{2max} (ml/k/min)	IgG (g/L)	+0.44	0.19	0.049•
Vo_{2max} (ml/k/min)	SBP (mm Hg)	-0.73	0.53	0.001•
Vo_{2max} (ml/k/min)	EO (%)	-0.53	0.28	0.016•

Submaximal endurance exercise seems to lower the risk of URTI in hypertensive patients. Karampour *et al*. (2017) in their study found that one bout high intensity interval exercise in aerobic form had a significant increase in IgA, IgG and IgM levels while one bout submaximal resistance exercise did not have a significant effect on these variables (22). It seems that the use of an aerobic or anaerobic energy system is an effective factor in the response to immunoglobulins. Also, in other studies, prolonged and severe activity has been shown to weaken the immune system and short-term activity has strengthened this system (13, 15). In general, it can be stated that, in addition to the energy system involved in the activity, the duration of activity is also an effective factor in the response to the adaptive immune system. The results of this study showed that

OBSEE caused a significant reduction in EO in hypertensive patients. EO is involved in inflammatory reactions, which causes the synthesis and release of proteins that stimulate the activity of the vessels and smooth muscle contraction. EO also stimulates and releases a number of vascular activators, including histamine, prostaglandin D2, and leukotriene C4 and D4 from mast cells and basophils (21). The results of Weng *et al*. (2011) showed that the increase in EO in the lung plays an important role in inflammation and stimulation of pulmonary hypertension (23). Overall, it can be concluded that an increase in EO can lead to an increased risk of hypertension as well as the risk of other cardiovascular diseases. Therefore, submaximal endurance exercise of 60 to 65% MHRR can be a cardiovascular protective against inflammatory effects caused by an increase in EO. The results of this study showed that OBSEE caused a significant decrease in WBCs in hypertensive patients. Changes in the amount of WBCs depend on the intensity and duration of the exercise (24). As soon as an organ is exposed to stress, the brain begins to release the neuroendocrine mediators to help the immune system (25). The intensity of exercise also increases the sympathetic activity and the release of catecholamines (26). Thus, as much as the intensity of activity increases, the levels of epinephrine and norepinephrine also increase, resulting into to an increase in WBCs' mobility in the immune system (27). It seems that the submaximal intensity can increase the response of WBCs in hypertensive patients. However, there was no significant change in NEUT, MONO and LYMPH responses in hypertensive patients following OBSEE. These results are not consistent with the findings of the study by Neves *et al*. (2015) which investigated the impact of high intensity exercise on LYMPH and MONO (28). The reason for this discrepancy seems to be related to the intensity of the submaximal exercise versus the maximal one. Lymphatic secretion organs are nerved by the sympathetic neural fibers that are responsible for the release of epinephrine and norepinephrine (24). Since LYMPH and MONO have a high concentration of beta receptors, (29) therefore, with increasing severity of activity and also increased epinephrine and norepinephrine secretion, beta receptors responses also increase and thus increase LYMPH and MONO as much as possible. Thus, it seems that the innate and adaptive immune system factors of hypertensive patients have different responses depending on the exercise intensity.

Conclusion

Performing OBSEE can improve the response of a large part of the adaptive immune system; consequently, in this study, the IgA, IgG and IgM responses increased in patients with high blood pressure. On the other hand, increased responses of other adaptive immune systems require high-intensity exercises. Therefore, it seems that stimulating the response of all the factors involved in the adaptive immune system of hypertensive patients requires performing exercise with varying degrees of intensity. Nonetheless, stimulating the response of all the innate immune system factors, like adaptive immunity, requires performing exercise with varying degrees of intensity. Because the exercise with sub-maximal intensity in these patients only changed the WBC and EO, while the response of other innate immune system factors in hypertensive patients did not change significantly. The considerable result related to the adaptive immunity of hypertensive patients is that submaximal endurance exercise has been able to reduce the cardiovascular risk associated with elevated EO in these patients.

Ethical issues

The study protocols and procedures had previously been approved by the Research Ethics Committee of Islamic Azad University, Omidiyeh Branch.

Authors' contributions

All authors contributed equally to the writing and revision of this paper.

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