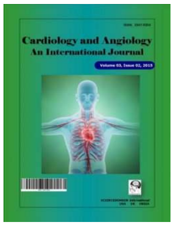

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The Effect of Long-term Aerobic Exercises on Autonomic Imbalance in Postmenopausal Women

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Authors' contributions

This work was carried out in collaboration between all authors. Authors AEDRAR and HMI designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author AHS managed the analyses of the study. Author MAA managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Objective: Study the effects of aerobic exercises on autonomic imbalance associated with menopausal women.

Methods: The study included twenty postmenopausal women (age 50.7± 0.86 mean ± SEM years old). All of them underwent 6 months of aerobic training program (3 sessions per week where every session is about one hour). Before and after the training program we measured the following parameters: 1) Heart rate variability indices using 24 hours ambulatory monitoring (Cardio Holter), both of time and frequency domain parameters were measured. 2) Serum levels of nitric oxide and catecholamines (adrenaline and noradrenaline). 3) Number of hot flashes per day.

Results: Six months of aerobic training program produced significant increase of all heart rate variability indices as compared with the starting levels: 1) Time domain parameters in the form of standard deviation of all normal RR intervals (SDNN), *P<0.0001*, and root mean square of

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successive RR intervals (rMSSD), *P<0.001*, where RR is the time between two successive R waves in the ECG. 2) Frequency domain parameters in the form of power in the low frequency range (LF), *P<0.001* and power in the high frequency range (HF), *P<0.0001*. Chemical analysis revealed significant increase in serum level of nitric oxide, *P < 0.0001* alongside with significant decrease in catecholamines levels (*P<0.0001*) for both adrenaline and noradrenaline) compared with the starting levels. Number of hot flashes per day was significantly decreased as compared to the starting number, *P<0.001*.

Conclusions: Regular moderate intensity aerobic exercises can induce significant improvement of the disturbed autonomic balance in postmenopausal women most probably through increasing NO production. The exercise would most likely have to be sustained in order to reduce long term risk.

Keywords: Aerobic exercises; menopause; heart rate variability; catecholamines; hot flashes.

1. INTRODUCTION

Postmenopausal women experience an increase in cardiovascular disease (CVD), cancer, and other metabolic diseases, which could be associated with both aging and changes in hormonal status [1]. Vasomotor symptoms (VMS), including hot flashes and night sweats, also considered as major problems facing postmenopausal women, Exact cause of VMS isn't known but autonomic imbalance which usually occur after menopause may be implicated [2].

Habitual participation in physical activity results in many health benefits, but the beneficial effects of regular physical activity on the adverse health effects that frequently accompany the menopausal woman has not been fully explored [3]. Changes observed in effect of physical activity include increase in production of NO [4]. NO plays an important protective role in the cardiovascular system, Moreover, NO has an important role in regulation of autonomic nervous system [5].

Heart rate variability (HRV) is a reliable method, which can be used as an index of cardiac autonomic balance. It is a noninvasive technique, based on electrocardiogram (ECG) thus providing a dynamic assessment of sympathetic and parasympathetic components of the autonomic nervous system [6]. Serum Catecholamines also considered good indicators of autonomic cardiovascular control [7].

The aims of our study were to determine the impact of moderate intensity aerobic exercises on NO production and to determine the association among NO, autonomic imbalance, and vasomotor symptoms in postmenopausal women.

2. PARTICIPANTS AND METHODS

2.1 Participants

The study protocol was approved by the local ethics committee and informed consent was obtained from all volunteers. Twenty postmenopausal sedentary females (age 50.7± 0.86 mean± SEM years old) were studied before and after 6 months of aerobic exercise training (Each women considered as menopausal one when she had a permanent cessation of menstruation for one year [8]. The average time since menopause was 4.4 year. None of these women participated in regular exercise for the last six months. All participants were free from cardiovascular diseases on clinical examination (normal ECG) and could safely participate in exercise. Women with diabetes mellitus, hypertension, or any other systemic diseases and malignancy were excluded from the study. None of the participants had used menopausal hormone treatments. Arterial blood pressure was measured by mercury sphygmomanometer and heart rate was calculated during ECG recording, these measurements were performed at a uniform time of the day and at comfortable circumstances and temperature.

2.2 Exercise Intervention

This prospective study was conducted at the Minia stadium (female sports center), Physiology, and Cardiology departments (Faculty of Medicine) of Minia University, MInia, Egypt during the period from June 2015 to February 2016. The women underwent exercise training under supervised conditions. They performed aerobic exercise training (3 sessions/ week, where every session was one hour for 24 week) at two different exercise intensities: a low-intensity for half an hour in the form of free aerobic exercises without tools (exercise gymnastic and dancing) and moderate intensity for the other half hour in the form of walking by using treadmill to control their heart rate and the intensity of walking [9].

2.2.1 Determination of exercise intensity

Low-intensity exercises produced 30 - 49% of maximal heart rate and moderate intensity exercises produced 50 - 69% of maxmal heart rate. Maximal heart rate is determined by the following equation: 220 – age in years [10].

2.3 Measurements

2.3.1 Heart rate variability analysis [11]

Holter recorders (Cardio Holter TM, Nasiff Associates Cardio Card TM, USA) were used for analysis of indices of heart rate variability for 24-hour for each women before and after the end of the program. Trained nurses applied the ECG leads, supervised monitoring, and downloaded data to the review station. All recordings were also examined visually and artifacts were deleted manually. All of the recordings had at least 22 hours of data once the artifacts were deleted. HRV parameters were calculated and statistically analyzed. Both the time- and frequency domain parameters of HRV were determined through analysis of the entire 24 hours recordings. Time-domain HRV parameters used in this study were chosen according to the guidelines of the European Society of Cardiology and the North American Society of Pacemaker and Electrophysiology, standard deviation of all normal RR intervals (SDNN), and root mean squared of successive RR intervals (rMSSD) were selected a time domain parameters. Frequency-domain HRV parameters used in this study were chosen according to the same guidelines, power in the low frequency range (LF: 0.04-0.15 Hz), and power in the high frequency range (HF: 0.15-0.4 Hz).

2.3.2 Laboratory investigations included

Measurement of serum nitric oxide and catecholamine's (adrenaline and nor-adrenaline) were obtained before and after the 6 months intervention.

2.3.2.1 Collection and preparation of the samples

Fasting blood samples were collected from every volunteer by sterile venipuncture in the morning on the beginning and after the 6 months of the program. Serum samples were stored at - 20℃ till the time of analysis.

- Determination of nitric oxide

  Serum nitric oxide was determined using kits for the Colorimetric determination of total nitrite (Biodiagnostic, Egypt). This assay determines the total nitric oxide based on the enzymatic conversion of nitrate to nitrite by nitrate reductase. The reaction is followed by a colorimetric detection of nitrite as an azo dye product of the Griess [12].

- Determination of Catecholamines: Serum catecholamines (epinephrine, norepinephrine) were determined spectrophotometrically as described by Ciarlone [13] using spectroflurophotometer (Shiaduz RF-5000, Japan):

  0.1 ml of serum was completed to 0.3 ml with 0.2 N acetic acid. 3 ml of cold acidified butanol was added and centrifuged for 5 minutes at 1000 r.p.m. To 2.5 ml of organic layer, 1.6 ml of 0.2 N acetic acid and 5 ml of n-heptane were added, mixed well for 30 seconds, and centrifuged for 5 minutes at r.p.m. The organic layer was aspired and discarded out. Then one ml of the aliquot was taken and used for fluorescence development. To one ml of the aliquot, 0.2 ml of 0.1 N EDTA solutions was added and mixed well. Catecholamines were then oxidized by addition of 0.1 ml of 0.1 N iodine. After exactly 2 minutes, the oxidation was stopped by addition of 0.2 ml of alkaline sulfite and exactly 2 minutes later, the pH of the solution was adjusted at about 5.4 by the addition of 0.2 ml of 5 N acetic acid. Epinephrine fluorescence was then read immediately at 410 nm (excitation wave length) and 500 nm (emission wave length). Norepinephrine was read at 380 and 480 nm after the mixture was heated in a boiling water bath for exactly 2 minutes.

- Estimation of the number of hot flashes

  Number of hot flashes per day was estimated for each women through validated questionnaire (Close-ended Questions).

2.4 Statistical Analysis

Data were represented as means ± standard errors of the mean (SEM). Statistical analysis was performed using Prism computer program (Graph pad Prism 6, software Inc., San Diego, CA, USA). Significant difference between groups was done by t test (non parametric tests) with a value of $P \leq 0.05$ considered statistically significant.

3. RESULTS

Regular aerobic exercises for six months in postmenopausal women significantly decreased resting heart rate (P<0.01) (Table 1). There were no significant changes in body mass index (BMI), systolic and diastolic blood pressure from baseline values.

Six months of regular aerobic exercises were significantly increased time domain parameters in the form of SDNN and rMSSD (*P*<0.0001 and *P* <0.001 respectively) (Fig. 1).

Six months of regular aerobic exercises significantly increased frequency domain parameters in the form of LF and HF (*P*<0.001 and *P*<0.0001 respectively) (Fig. 2).

Six months of regular aerobic exercises significantly increased Serum concentration of nitric oxide (*P<0.0001)* (Fig. 3).

Table 2 Number of hot flashes per day and serum levels of epinephrine and norepinephrine were significantly decreased following Six months of regular aerobic exercises in postmenopausal women.

Table 1. Mean ± SEM values of anthropometric and clinical data before and after six months of aerobic exercises in post menopausal women

Variables	Before	After	P value
BMI (kgm^2)	31.70 ± 0.43	30.40 ± 0.66	*0.08*
Heart rate (bpm)	77.35 ± 1.05	74.20 ± 0.82*	*0.01*
Systolic blood pressure (mmHg)	127.8 ± 1.42	126.8 ± 1.16	*0.29*
Diastolic blood pressure (mmHg)	83 ± 0.98	81.50 ± 0.68	*0.09S*

Data of twenty postmenopausal women *******: *significant from the starting level. P≤0.05. BMI: body mass index bpm: beat per minute*

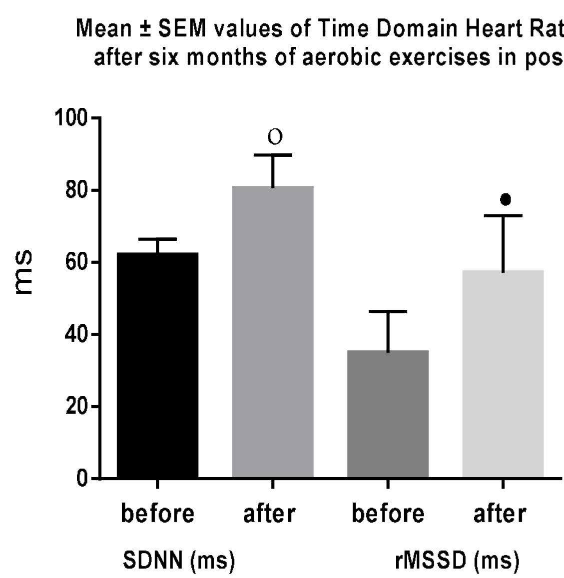

Fig. 1. Data of twenty postmenopausal women
● o: Significant from the starting level. P≤0.05

Table 2. Mean ± SEM values of hot flashes and serum catecholamines before and after six months of aerobic exercises in post menopausal women

Time / Parameter	Before	After	P value
No. of hot flashes per day	9.2± 0.43	2.35± 0.22•	*0.001*
Serum epinephrine level Pg/ml	27.60± 0.94	20.70± 0.52•	*0.0001*
Serum norepinephrine level Pg/ml	326.5± 6.677	247.4± 6.077•	*0.0001*

Data of twenty postmenopausal women ●: significant from the starting level. P≤0.05

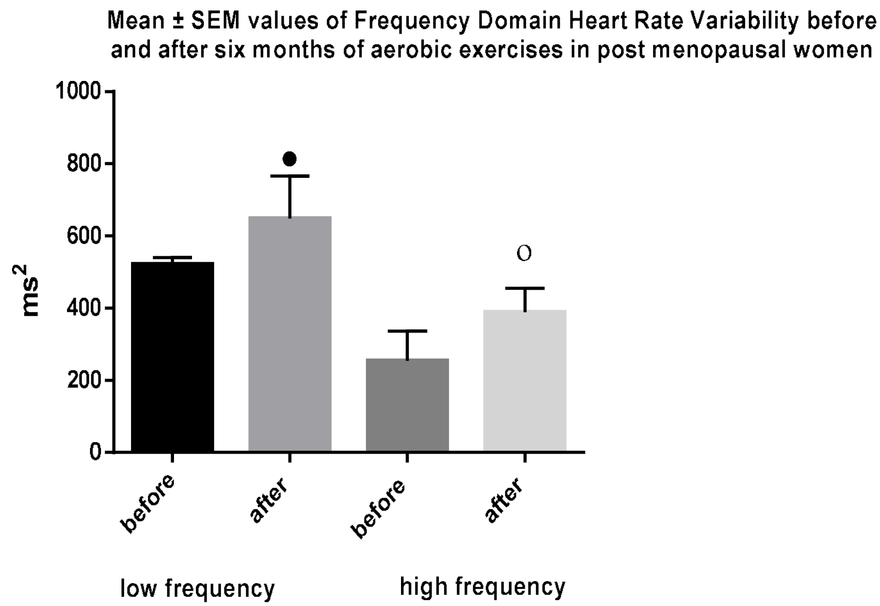

Fig. 2. Data of twenty postmenopausal women
● o: significant from the starting level. P≤0.05

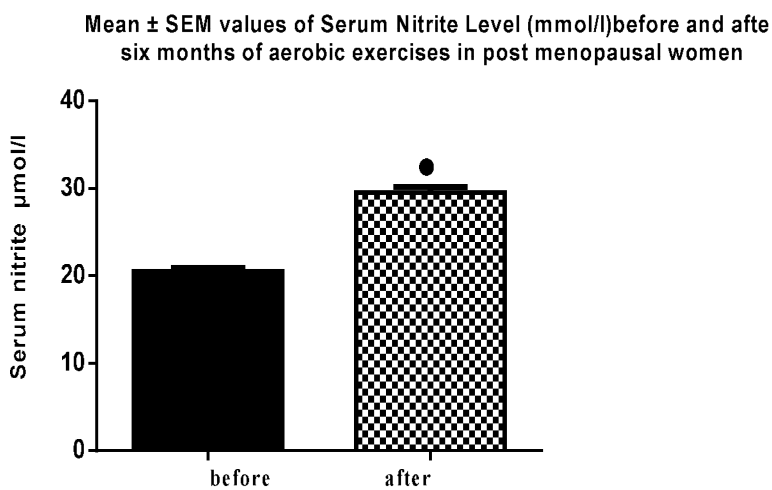

Fig. 3. Data of twenty postmenopausal women
●: significant from the starting level. P≤0.05

4. DISCUSSION

A reduction in ovarian hormones after menopause causes an autonomic imbalance and increases the risk of cardiovascular diseases [14]. Autonomic cardiovascular control can be evaluated using heart rate variability analysis, and plasma catecholamines [7]. Menopause is also associated with vasomotor symptoms (also known as hot flashes). The cause for these vasomotor symptoms is not fully understood, although some theories have been proposed [15].

Although many indices of HRV exist, the time and frequency domain indices are the most common. For the time domain, the root mean square of successive RR intervals (rMSSD) represents parasympathetic nervous system activity, and the standard deviation of normal beat-to-beat (RR) intervals (SDNN) is a global index encompassing both the sympathetic and parasympathetic nervous systems. For the frequency domain, high frequency (HF, 0.15–0.40 Hz) power has been linked to vagal activity [16].

Based on these findings, we aimed to evaluate the autonomic nervous system in twenty postmenopausal sedentary women before and after six months of aerobic exercise program. We used both non invasive easy technique (Cardio Holter) to measure heart rate variability indices and confirmed our results by their related biochemical parameters.

The results of our study showed significant increase in all heart rate variability indices and a significant decrease in resting heart rate from baseline values. Moreover, there were significant decrease in catecholamines levels and a significant increase in serum nitric oxide level from baseline values.

The significant decrease in resting heart rate alongside significant increase in HRV indices are in agreement with Jurca et al. [17] who reported the effects of 8 weeks of moderate intensity aerobic exercise training on 49 postmenopausal women. Also, the significant increase in both SDNN and rMSSD are in agreement with Aubert et al [18] who reported significant improvement of both parameters after aerobic exercises in 10 postmenopausal women. Our findings were also in agreement with that reported by Earnest et al. [3] who reported a significant increase in rMSSD in postmenopausal women aged > 60 years after 6 months of exercise. These results can be explained by improvement of the symapathovagal balance after the training. In contrast to our study Davy et al. [19] reported that HRV did not improve after 12 weeks of aerobic exercise at 70% of maximal heart rate in postmenopausal women. The difference between their findings and ours can be explained by short duration of their exercise program. Our results are also in agreement with Crisafulli et al. [20] who said that increased sympathetic tone and decreased parasympathetic activity have been often reported in patients with chronic heart failure (CHF). Exercise training programs induces beneficial effects on autonomic function in those patients as threshold intensity exercises affected cardiac autonomic function and produce positive effects on sympathovagal balance.

In our work, the significant increase in serum levels of nitric oxide as compared with the baseline values were in agreement with De Oliveira et al. [1], who reported that aerobic exercise for 12 weeks on type 2 diabetic male and female human subjects provided important upregulation in antioxidant enzymes and increased nitric oxide bioavailability, which may help minimize oxidative stress and the development of the chronic complications of diabetes. During exercise Shear stress which occur on endothelial cells considered as a potent stimulus for NO production [21].

Many previous researches tried to investigate the role of NO on HRV, Hasan et al. [22] reported that in patients with Coronary slow flow, decreased plasma NO may cause the decrease in HRV by decreasing myocardial blood flow. NO may play a role in increasing cardiac vagal control and, in doing so, may indirectly inhibit sympathetic influences [23]. Exercise training has been found to improve endothelial function and NO bioavailability [24] among individuals with coronary risk or coronary atherosclerosis. Therefore, it is possible that the relationship between exercise and cardiac vagal activity is mediated, at least in part, by NO. Functionally, NO has been shown to increase neuronal activity within central sites regulating parasympathetic outow to the heart [25]. Peripherally, NO potentiates the bradycardic effects of parasympathetic stimulation [26] and also enhances the ability of the efferent vagus to antagonize sympathetic cardiac responses, with both pre and post-synaptic mechanisms postulated [27].

In our study, the significant increase of NO is associated with a significant decrease in catecholamines. These results are in agreement with Javier et al. [28] who studied the effect of aerobic exercise training on sympathetic, nitrergic and sensory innervations function in superior mesenteric artery from spontaneously hypertensive rats and they found that aerobic exercise training decreases contractile response to electrical field stimulation in mesenteric artery from spontaneously hypertensive rats. This effect is the net result of decreased both noradrenaline release, sensitivity to the vasoconstrictive effects of noradrenaline and increased neuronal nitric oxide release and bioavailability.

So in our study, significant increase in HRV plus significant decrease in catecholamines insure shift of the balance of the autonomic nervous system towards the parasympathetic side. The effect which could be produced as a result of increased NO production by the stimulus effect of long term exercise.

Six months of regular aerobic exercise significantly reduced the frequency of hot flashes. These results are in agreement with Elavsky and McAuley [2] who have tested the effect of physical activity (generally aerobic exercises) on VMS among 164 previously sedentary women randomized either to a walking group, yoga, or a control group. Although the etiology of the hot flashes is still not fully understood, neuroendocrine processes at the level of the hypothalamus are implicated. Miller and Li [29] reported that physical activity has a range of neuroendocrine responses that occur both acutely, as a result of a single bout of exercise, and chronically, as a result of exercise training. Increases in brain norepinephrine and its metabolites occur in response to acute exercise [30], but 24-hour urinary norepinephrine seems to decrease with training perhaps because of an increase in vagal tone [31]. Hot flashes may result from an imbalance in the autonomic nervous system, in which the “stress-buffering” role of the parasympathetic nervous system is not adequate to counter the increased activation of the sympathetic nervous system. Then the shift in that balance as a result of exercise training is a potential mechanism by which exercise could reduce the occurrence of VMS [32]. This could explain the reduction in the frequency of hot flashes in our work.

5. CONCLUSION

In conclusion, our study ensured the critical role of long term regular aerobic exercises in fighting many of menopausal problems. Shifting of autonomic balance in favor of the parasympathetic nervous system (as approved by HRV indices and serum catecholamines) could decrease the risk of cardiovascular diseases and improve VMS.

6. RECOMMENDATIONS

Physical activity is a potent tool for health promotion and disease prevention in postmenopausal women. Unfortunately, only few of postmenopaual women in Egypt regularly participate in physical activity at even the minimal level required for health benefits. This proportion may be even lower, depending on how physical activity is assessed. These data present a clear mandate to clinicians and public health professionals alike. All clinicians should prescribe regular physical activity to their patients and should be prepared to discuss and solve problems that exist with their patients to becoming more physically active. In Egypt women face economic and cultural barriers that prevent them from participating in exercise. However, creative solutions should be developed as regular physical activity can help in decrease VMS, and produce other health benefits that it confers on midlife women and ensure both a healthy menopausal transition and healthy aging.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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