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Research Paper

Influence of aerobic exercise training on cardiovascular and endocrine-inflammatory biomarkers in hypertensive postmenopausal women☆

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ABSTRACT

Given that few studies have examined the interaction between endocrine-inflammatory mediators and aerobic exercise training in hypertensive postmenopausal women, the aim of this study was to investigate whether aerobic exercise training (AET) for twenty-four sessions would alter cortisol, leptin and interleukin-1β (IL-1β) levels. To further analyze endothelium function in response to AET, we also examined redox state as well as NO/cGMP pathway in this population. Eighteen hypertensive postmenopausal women finished this study. AET program consisted of 24 sessions in treadmill, 3 times per week, duration of 30 up to 40 min for each session, for 8 weeks at intensity of 100% of the MLSS according to previous incremental test. Heart rate was monitored in all studied time (resting and during exercise sessions). After 48 h of the last exercise session, blood samples were collected for biochemical analyses (levels of cortisol, leptin, IL-1β, nitrite/nitrate (NOx^-), cGMP, malondialdehyde (MDA) and asymmetric dimethylarginine (ADMA); superoxide and catalase activity). We also measured systolic and diastolic blood pressure. A significant reduction in body mass was observed. As expected, systolic and diastolic blood pressure values were significantly reduced after AET in hypertensive women. We also found a marked increase in NOx^- levels as well as cGMP concentration in trained women, approximately 37.7 and 30.8%, respectively. No changes in cortisol, leptin, ADMA and IL-1β levels were observed after AET. Similarly, MDA levels and catalase activity were not affected by AET. In contrast, a marked increase in SOD activity was found (86.6%). In conclusion, our findings show that aerobic exercise training for twenty-four sessions promoted a significant reduction in blood pressure by activating NO/cGMP pathway as well as by promoting an up-regulation of SOD activity without changing in cortisol/leptin levels in postmenopausal hypertensive women.

Introduction

Epidemiological studies have shown that the incidence of cardiovascular diseases (CVD) in women increases dramatically after menopause [1,2]. However, the underlying mechanisms are not yet fully clarified. Several hypotheses have been proposed to explain this phenomenon in postmenopausal women. Estrogen deficiency has been pointed out to play a major role, but its deficiency partially explains the increased incidence of CVD since hormone replacement therapy did not prevent or mitigated cardiovascular events in this population [3,4]. Oxidative stress is another explanation, where increased production of the inflammatory mediators would lead to a massive production of reactive oxygen species, which in turn, resulting in endothelium dysfunction with decrease in nitric oxide (NO) production or its bioavailability to the cells [5]. However, some studies found a positive association between CVD and inflammatory mediators [6–8] whereas others failed to detect any association [9] in climacteric phase. The hypothalamic-pituitary-adrenal axis has also been linked to the higher incidence of CVD in postmenopausal women [10,11]. Nevertheless, the number of studies examining the interaction between menopause status and glucocorticoids is scarce.

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Therefore, the higher incidence of CVD in postmenopausal women still a complex issue and further studies should be carried out to look at the insight mechanisms as well as to get more information in an attempt to prevent cardiovascular events in this population. On the other hand, a plethora of studies has shown that physically active subjects have more longevity with reduction of morbidity and mortality [12,13]. Given that few studies have examined the interaction between endocrine-inflammatory mediators and aerobic exercise training in hypertensive postmenopausal women, the aim of this study was to investigate whether aerobic exercise training for twenty-four sessions would alter cortisol, leptin and interleukin-1β levels. To further analyze endothelium function in response to exercise training, we also examined redox state as well as NO/cGMP pathway in this population.

Methodology

Study participants

This study was approved by the Ethical Committee of Institute of Bioscience at the University of São Paulo State (UNESP). All the volunteers were recruited through advertisements in the surrounding area of UNESP. A total of thirty-two volunteers were eligible to participate in the study. After all screening test, only eighteen women finished the study. Postmenopausal status was determined as the absence of menstruation for at least 1 year under natural or surgical causes were classified as hypertensive according to previous medical diagnosis (systolic blood pressure: 140–159 mm Hg, diastolic blood pressure: 90–99 mm Hg or using anti-hypertensive). The inclusion criteria of this study were: to be hypertensive; body mass index $\leq$30 kg/m^2; sedentary ($<$150 min of moderate physical activity per week or $<$60 min of vigorous physical activity per week). The exclusion criteria were: smoking, taking hormone replacement therapy, diabetic, cardiovascular disease (stroke, heart failure); renal dysfunction; other condition that precludes the practice of physical exercise. Before starting the protocol, volunteers were informed about the procedures and risks of the study and signed a consent form in accordance with Ethical Committee of UNESP.

Study protocol

This clinical trial lasted 10 weeks and all parameters were evaluated at initial time and after 24 sessions of the aerobic exercise training (AET). Initially, the anthropometric and cardiovascular parameters were measured and volunteers were familiarized to the treadmill during 2–4 days, depending upon each participant. After familiarization, maximal lactate steady state (MLSS) was defined individually for prescription of AET intensity. Briefly, postmenopausal women performed two to five tests with fixed duration (30 min) and walking speed (5.5 km/h) on a treadmill (Movement RT 250 PRO) in accordance with previous study [14]. The inclination of the ergometer was used to control the intensity that ranged between 1 and 15%. The intensity was adjusted in each test according to the aerobic capacity of the participant. Measurement blood lactate concentration was performed at rest, 10th and 30th min during incremental test. MLSS was determined when the difference of blood lactate concentration between 10th and 30th min was not exceeded 1 mM [15].

AET program consisted of 24 sessions in treadmill, 3 times per week, duration of 30 up to 40 min for each session, for 8 weeks. The intensity of the AET was 100% of the MLSS according to previous incremental test. Heart rate was monitored and AET was supervised by exercise physiologists in an environmental with temperature ($\approx$25 °C) and humidity (40–60%) controlled. Figure 1 illustrates the experimental design.

Anthropometric parameters

Body weight and height was determined using a scale and stadiometer (Toledo 2096 PP). Body mass index was calculated as the ratio body weight divided by the square of the height in meters. Waist circumference was measured at the midpoint between the last rib and iliac crest.

Cardiovascular parameters

Blood pressure (BP) – After 20 min of sitting position, three consecutives BP measurements using a semi-automatic equipment (Microlife MIB-P3BTOA). Resting BP was determined as the average of the measurements.

Heart rate (HR) – HR was measured using a heart rate monitor (Polar FT1 TRQ) after 20 min of seated position. At the final of the resting period the value of HR was obtained.

Blood samples

Blood samples were collected after 12 h of overnight fast (between 7:00 and 8:00 am). Blood samples were collected from the antecubital vein using standard venipuncture methods. Samples were centrifuged (3000 rpm, 12 min) and the supernatant (plasma and serum) were stored in aliquots at −80 °C for future analysis.

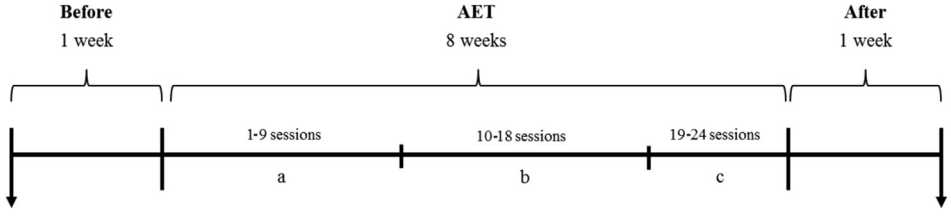

Figure 1. Experimental design.

Table 1
Effects of aerobic exercise training on anthropometrical parameters, lipid profile, glycemia and MLSS in hypertensive postmenopausal women.

Parameters ($n = 18$)	Initial	Final
Age (yrs)	58.3 ± 1.2	–
Time after menopause (yrs)	10.3 ± 2.1	–
BMI	27.3 ± 0.5	26.9 ± 0.5*
WC	94.4 ± 1.6	93.4 ± 1.5*
TC (mg/dL)	195.4 ± 6.4	194.1 ± 5.5
LDL-c (mg/dL)	124.7 ± 6.4	124.2 ± 5.0
HDL-c (mg/dL)	46.9 ± 1.7	49.1 ± 1.5
VLDL-c (mg/dL)	23.8 ± 1.9	20.6 ± 1.5
TG (mg/dL)	113.8 ± 10	103.1 ± 7.8
Glycemia (mg/dL)	87.2 ± 2.2	90.3 ± 2.1
Rest HR	67.3 ± 2.7	64.7 ± 2.2*
MLSS exercise HR	152 ± 4.7	151 ± 5.1
MLSS threshold	5.5 ± 0.4	7.3 ± 0.5*

BMI = body mass index (kg/m^2); WC = waist circumference (cm); TC = total cholesterol; LDL = low density lipoprotein; HDL = high-density lipoprotein; VLDL = very low-density lipoprotein; TG = triglycerides. HR = heart rate (bpm); MLSS = maximal lactate steady state; Data are mean ± SEM.
*$P < 0.05$ compared with initial time.

Biochemical analyses

Lipid profile and glycemia – Serum concentrations of total cholesterol, low-density lipoprotein-cholesterol, very low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides and glycemia were determined using automated standard method (Cobas Mira Plus).

Cortisol – Serum concentrations of cortisol were measured by the chemiluminescence (ADVIA Centaur®). This is a competitive immunoassay that uses direct chemiluminescent technology.

Leptin – Serum leptin concentrations were measured by ELISA using a commercial available kit (SPI Bio, Montigny-le-Bretonneux, France) according to the manufacturer's instructions.

Interleukin-1β (IL-1β) and guanosine cyclic monophosphate (cGMP) – Plasma concentrations of IL-1β and cGMP were measured by ELISA using a commercial available kit (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions.

Asymmetric dimethylarginine (ADMA) – Plasma concentrations of ADMA were measured by ELISA using a commercial available kit (Immunodiagnostik AG, Bensheim, Germany) according to the manufacturer's instructions.

Nitrite/Nitrate (NO_x^-) – Plasma concentrations of NO_x^- were measured to evaluate NO production by commercial available kit (Cayman Chemical, Ann Arbor, MI, USA) according to the manufacturer's instructions. Before starting this assay samples were ultrafiltered through micro filter (Microcon Centrifugal Filter Units, 10 kDa, Millipore, Bedford, MA).

Superoxide dismutase (SOD), catalase and malondialdehyde (MDA) – All these markers were measured by ELISA using a commercial available kit (Cayman Chemical, Ann Arbor, MI, USA) according to the manufacturer's instructions. SOD's assay detects radicals superoxide generated by xanthine oxidase and hypoxanthine, revealing the plasmatic activity of this enzyme. Catalase's assay is based on the reaction of the enzyme with methanol in an optimal H_2O_2 concentration. Serum levels of MDA were determined to evaluate lipid peroxidation [16].

Statistical analysis

Data are presented as mean ± standard error mean. Normality of the data was verified by the Kolmogorov–Smirnov's test. A paired Student's *t*-test was used to analyze the effect of AET on the cardiometabolic and endocrine parameters. For all analyses, $P < 0.05$ was considered statistically significant.

Results

Body mass index values were significantly reduced in hypertensive postmenopausal women after 24 sessions of AET approximately 1.5% as compared to initial time. However, no changes were found in waist circumference, lipid profile and glycemia. On the other hand, the intensity of physical exercise employed in our study was effective to promote a significant increase in MLSS after AET, approximately 32.7%. Data are summarized in Table 1. Regarding antihypertensive therapy, 67% of the participants were on renin-angiotensin inhibitors or AT1 receptor blockers whereas six volunteers were on diuretics or beta-adrenergic receptor blocker therapy (33%). Regarding hypolipidemic compound, 50% of the volunteers were on therapy previously to the study.

As expected, AET was effective in lowering arterial blood pressure in trained HT women, approximately −3.8% and −5.9% for systolic and diastolic blood pressure, respectively (Figure 2, panels A and B). Resting heart rate values were also decreased after 24

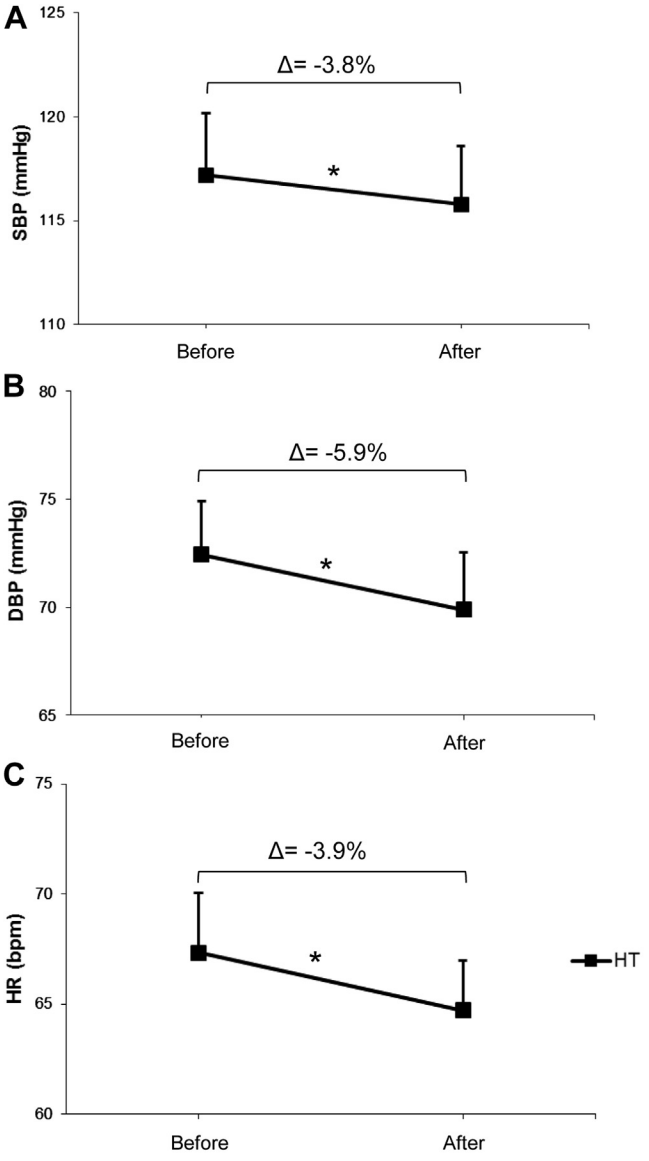

Figure 2. Effects of aerobic exercise training on systolic blood pressure (SBP, panel A), diastolic blood pressure (DBP, panel B) and resting heart rate (HR, panel C) in postmenopausal hypertensive women ($n = 18$). *$P < 0.05$ paired *t* test between initial and final time of the study.

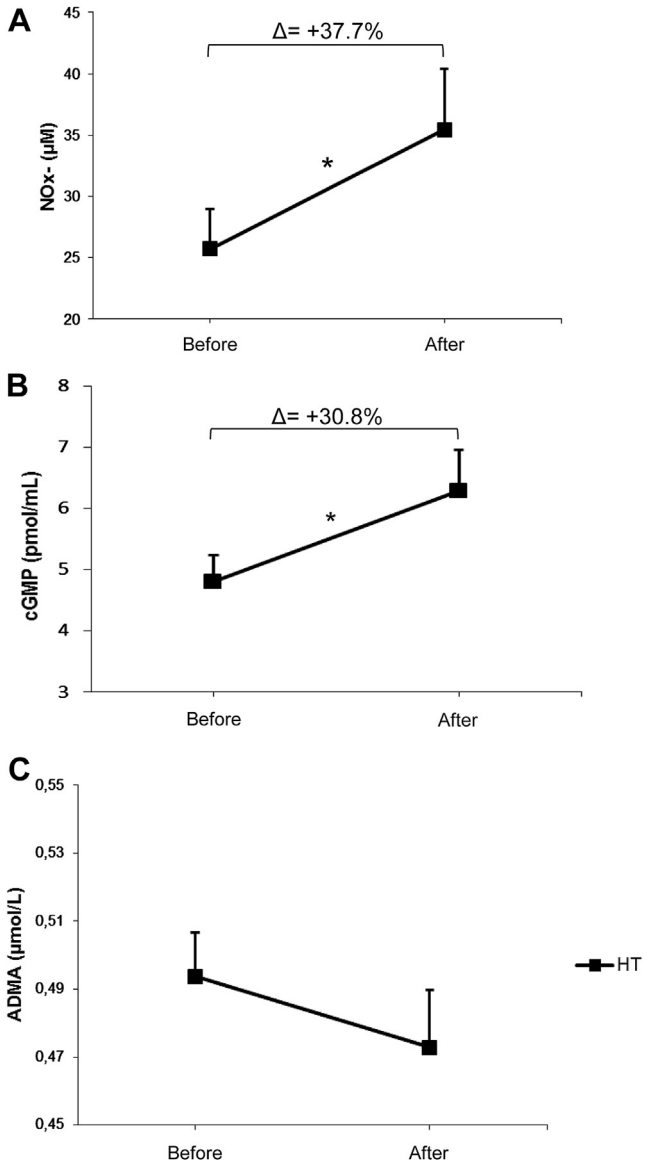

Figure 3. Effects of aerobic exercise training on NOx^- (panel A), cGMP (panel B) and ADMA (panel C) levels in postmenopausal hypertensive women ($n = 18$). *$P < 0.05$ paired t test between initial and final time of the study.

sessions of aerobic physical exercise (Table 1 and Figure 2C). Given that it is well established that the health beneficial effect of the exercise training is related to activation of NO/cGMP signaling pathway, we have evaluated these biomarkers before and after twenty-four sessions of aerobic physical exercise. We found a marked increase in NOx^- levels, which reflect NO production, as well as cGMP concentration in trained women, approximately 37.7 and 30.8%, respectively (Figure 3, panels A and B). Interestingly, we found no changes in ADMA levels (Figure 3C).

Furthermore, we also analyzed the redox state by measuring SOD and catalase activities and MDA concentration. Our findings show that AET promoted a profound increase in SOD activity, approximately 86.6% (Figure 4A). No changes were found catalase activity and MDA concentration (Figure 4, panels B and C).

Regarding endocrine-inflammatory mediators, we found no effects of the AET on cortisol, leptin and IL-1β levels in postmenopausal hypertensive women (Figure 5, panels A, B and C, respectively). Interestingly, we found a positive relationship between systolic blood pressure values and cortisol levels at initial time of the study ($r^2 = 0.2422$, $P < 0.0448$, $n = 17$, Figure 6A) whereas this correlation was abrogated after AET ($P > 0.05$, Figure 6B).

Discussion

A number of studies have shown that cardiovascular diseases can be prevented by regular physical exercise either in human or in laboratory animals, which is strongly associated with an increase in NO bioavailability [17–19]. Regarding postmenopausal women, recent study found that aerobic exercise training even in a low intensity promoted reductions in blood pressure showing how changing in the lifestyle is favorable for this particular population in preventing cardiovascular events [20]. However, no mechanist

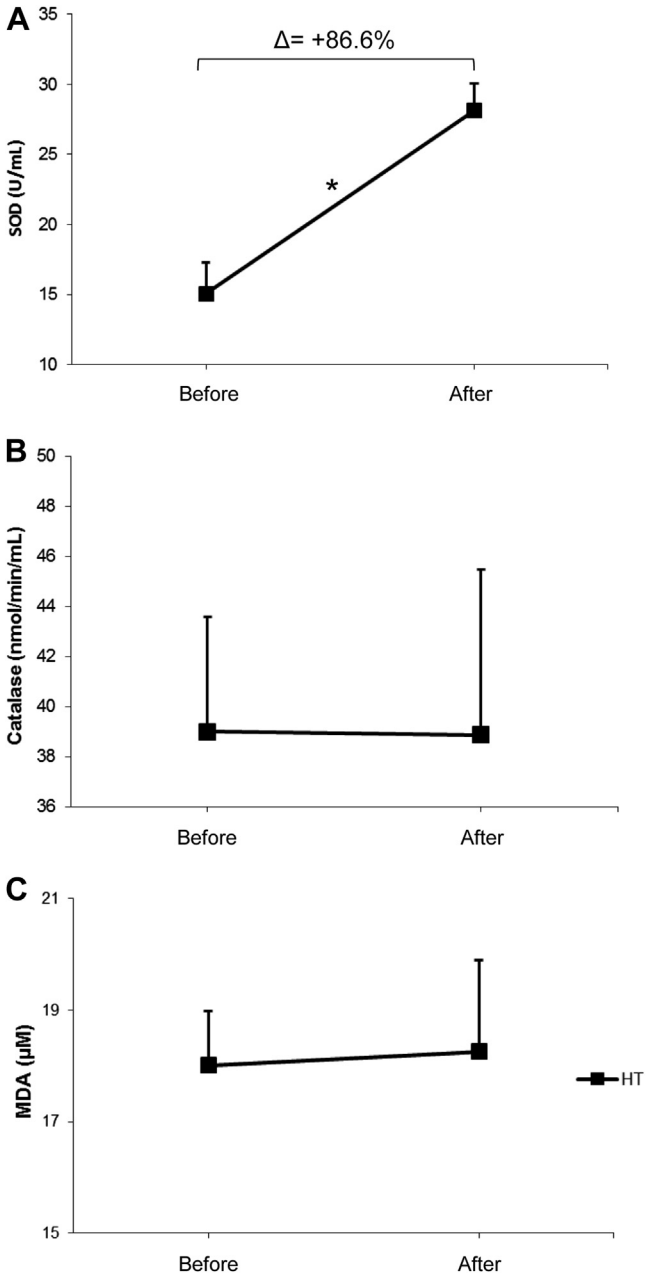

Figure 4. Effects of aerobic exercise training on SOD (panel A), catalase (panel B) activity and MDA concentration (panel C) in postmenopausal hypertensive women ($n = 18$). *$P < 0.05$ paired t test between initial and final time of the study.

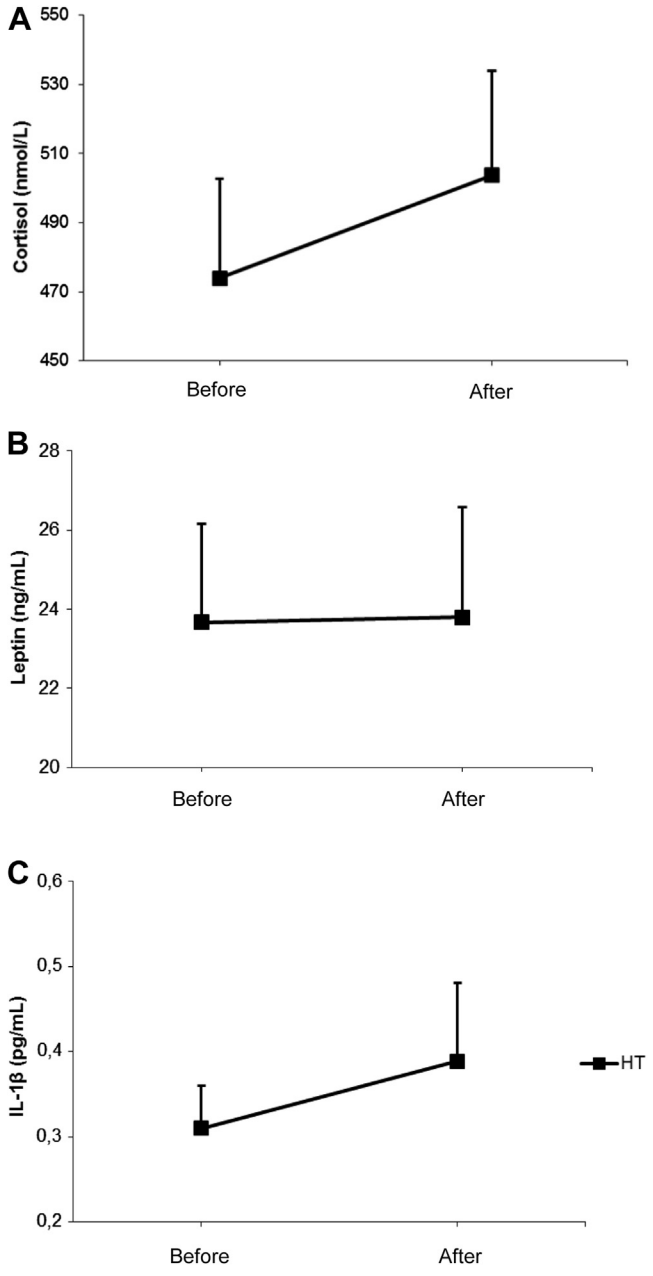

Figure 5. Effects of aerobic exercise training on cortisol (panel A), leptin (panel B) and IL-1β levels (panel C) in postmenopausal hypertensive women ($n = 18$). $^{*}P < 0.05$ paired t test between initial and final time of the study.

events have been reported. Thus, one of the objectives of our study is to examine different pathways that regulate blood pressure in response to exercise training in hypertensive postmenopausal women. We found that twenty-four sessions of aerobic physical exercise was effective in reducing BMI as well as to improve the physical capacity of all volunteers. Additionally, the reductions of systolic and diastolic blood pressure were positively associated with an improvement of NO/cGMP pathway as well as an up-regulation of SOD activity. Taken together, these findings show that aerobic exercise training promoted an improvement of endothelium function in hypertensive postmenopausal women. Indeed, previous studies from our group have systematically demonstrated the beneficial effects of the exercise training on cardiovascular system by increased production of NO and/or its bioavailability in postmenopausal women [21–24]. To further examine the association between NO inhibition and hypertension in postmenopausal women, we looked at ADMA levels since evidences have linked increased ADMA levels in patients with angina, arterial hypertension and immune dysfunction mainly in elderly and postmenopausal women [25–27]. We found no changes in ADMA levels in trained women excluding the contribution of this endothelial pathway on the beneficial effects of exercise training in blood pressure regulation. In contrast, two recent studies from the same group showed a decrease in plasma ADMA in healthy postmenopausal women in response to aerobic exercise training as well as an inverse relationship between aerobic fitness and levels of ADMA [28,29]. However, these studies did not measure NO production, and blood pressure values were not modified by exercise training. Thus, more studies should be carried out to check the contribution of the endogenous inhibition of NO availability on arterial hypertension as well as the effects of exercise training on ADMA/NOS pathway.

Increased oxidative stress has been pointed out to play an important in the pathogenesis of arterial hypertension in men [30] as well as in postmenopausal women [5,31]. Although evidences have demonstrated that trained [32] or physically active healthy postmenopausal women [33] showed a decreased in circulating concentrations of MDA as compared to sedentary one, no blood pressure measurements were performed in these studies. Thus, the data do not clarify the high incidence of arterial hypertension in postmenopausal women or explain the insight mechanisms in the phenomenon. In our study, we found no changes in MDA levels in response to exercise training in hypertensive postmenopausal women excluding the contribution of this biomarker in the beneficial effects of physical exercise on blood pressure regulation. We also found no changes in the pro-inflammatory mediators, IL-1β and leptin, in response to exercise training. It has been reported the influence of estrogen on pro- and anti-inflammatory pathway in different cells types [34]. Indeed, in whole human blood cultures, the addition of different concentration of estrogen decreases secretion of several pro-inflammatory mediators, mainly IL-1β [35]. Additionally, it has been demonstrated an increase in inflammatory mediators in experimental model of menopause [36]. Interestingly, a previous study showed that IL-1β levels increase in the early stage of the menopause (less than five years) and return to the normal levels in the late stage, with values similar to premenopause phase [8]. Thus, it is not clear whether estrogen deficiency could lead to an inflammatory state in postmenopausal women. Furthermore, the range of concentration of IL-1β levels in women is very wide varying between 0.30 and 0.081 pg/mL depending on the reproductive phase or not as well as the time after menopause [37]. Regarding leptin levels and postmenopausal women, the interaction is even more complex [38]. An increase [39], no variation [40] and a decrease [41,42] in circulating leptin levels were detected after menopause. Previous studies reported that postmenopausal women under caloric restriction [43] or on tibolone therapy [42] showed a significant reduction in leptin levels. In our study, exercise training did not affect leptin levels even though there was a slight reduction in the BMI (1.5%). Indeed, previous studies have shown that changes in leptin levels are detected only when physical training is associated with caloric restriction in postmenopausal women [44,45].

A number of studies have shown the importance of cortisol, the major glucocorticoid hormone produced in human, in elevating blood pressure [46–48]. Several signaling pathways seem to be involved in the mechanisms by which cortisol produces arterial hypertension including sodium/volume homeostasis, activation of the renin-angiotensin system, and increased sympathetic drive [49–52]. Additionally, it has been reported that cortisol impairs NO production measured by NOx^{-} levels attributing thus, the cortisol-induced hypertension to the NO deficiency in both human and experimental

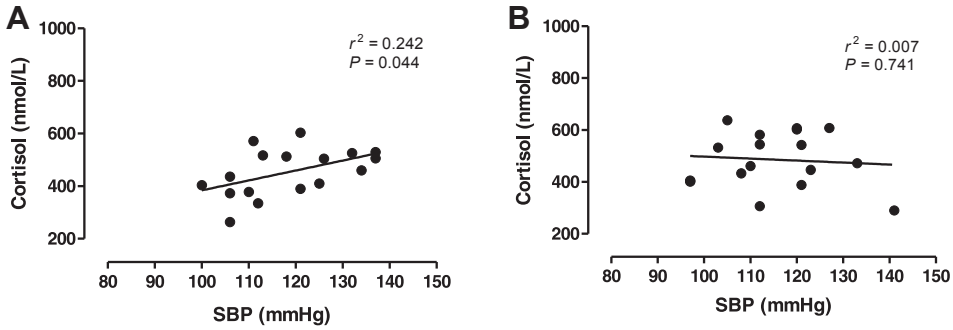

Figure 6. Correlation between systolic blood pressure values and cortisol levels at initial time (panel A) and after twenty-four sessions (panel B) of physical exercise in postmenopausal hypertensive women.

model [53,54]. However, most of the studies have examined the interaction between cortisol and arterial hypertension in male subjects [55] and no one examined the effects of exercise training on endocrine-inflammatory mediators in hypertensive postmenopausal women. In our study, we found no effects of the exercise training in the cortisol concentration in hypertensive postmenopausal women. Thus, it is clear that the beneficial effects of exercise training on blood pressure were related to an improvement of NO/cGMP pathway without changing in serum cortisol levels. This is confirmed by the lack of positive correlation between cortisol and blood pressure after twenty-four sessions of exercise. Collectively, our findings show that the endocrine-inflammatory mediators: cortisol, leptin and IL-1β did not contribute to the beneficial effects of the exercise training on blood pressure in hypertensive postmenopausal women. Furthermore, our study confirms that aerobic exercise training for twenty-four sessions promoted a reduction in blood pressure by activating NO/cGMP pathway as well as by promoting an up-regulation of SOD in this particular population.

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