



Aerobic training abolishes ambulatory blood pressure increase induced by estrogen therapy: A double blind randomized clinical trial

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ABSTRACT

Emerging data reveal that oral estrogen therapy can increase clinic blood pressure (BP) in post-menopausal women; however, it is important to establish its effects on ambulatory BP, which is a better predictor for target-organ damage. Besides estrogen therapy, aerobic training is widely recommended for post-menopausal women, and it can decrease ambulatory BP levels. This study was designed to evaluate the effect of aerobic training and estrogen therapy on the ambulatory BP of post-menopausal women. Forty seven healthy hysterectomized women were randomly divided (in a double-blind manner) into 4 groups: placebo-control (PLA-CO=12), estrogen therapy-control (ET-CO=14), placebo-aerobic training (PLA-AT=12), and estrogen therapy-aerobic training (ET-AT=09). The ET groups received estradiol valerate (1 mg/day) and the AT groups performed cycle ergometer, 3×/week at moderate intensity. Hormonal status (blood analysis), maximal cardiopulmonary exercise test (VO₂ peak) and ambulatory BP (24-h, daytime and nighttime) was evaluated before and 6 months after interventions. A significant increase in VO₂ peak was observed only in women who participated in aerobic training groups (+4.6 ± 1.0 ml kg⁻¹ min⁻¹, *P*=0.00). Follicle-stimulating hormone was a significant decreased in the ET groups (−18.65 ± 5.19 pg/ml, *P*=0.00), and it was accompanied by an increase in circulating estrogen (56.1 ± 6.6 pg/ml). A significant increase was observed in the ET groups for daytime (*P*=0.01) and nighttime systolic BP (*P*=0.01), as well as nighttime diastolic BP (*P*=0.02). However, daytime diastolic BP was increased only in the ET-CO group (+3.4 ± 1.2 mmHg, *P*=0.04), and did not change in any other groups. No significant effect was found in ambulatory heart rate. In conclusion, aerobic training abolished the increase of daytime ambulatory BP induced by estrogen therapy in hysterectomized, healthy, normotensive and postmenopausal women.

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1. Introduction

Menopause is a holistic process that involves many physiological changes, affecting not only the reproductive tissues but also other women's systems [1,2]. To handle many of the abnormalities that occur during this period, estrogen therapy has been widely employed [3], and it is mainly recommended for women who are at the beginning of the post-menopausal period [4].

In regard to the cardiovascular system, the post-menopausal period is accompanied by an increase in blood pressure (BP) [5]. Estrogen therapy produces controversial results in this aspect, increasing [6,7], decreasing [8,9] or not affecting [10,11] BP. Part

of this variability is attributable to women's ages. Steiner et al. [12] demonstrated that oral estrogen therapy might increase BP in 50-year-old women and decrease it in 70-year-old women. Ambulatory BP has been reported as a better cardiovascular prognostic index than clinic BP [13]. The effects of estrogen therapy on ambulatory BP have been poorly studied, and results are also controversial [14]. Tuomikoski et al. [6] verified in asymptomatic post-menopausal women that oral estradiol had a potential harmful cardiovascular effect by increasing ambulatory BP.

Aerobic training has been emphatically recommended to delay or prevent rising BP [15,16]. A recent meta-analysis concluded that for the general population the aerobic training is effective in reducing clinic and daytime systolic/diastolic BP in approximately −3.0/−2.4 and −3.3/−3.5 mmHg, respectively [17]. In post-menopausal women, Seals et al. [18] also observed a decrease in ambulatory BP after aerobic training, but these authors studied hypertensive women, and did not evaluate the interaction with estrogen therapy. In fact, to our knowledge, no previous study

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has investigated the association of these interventions in post-menopausal women's BP.

Based on the previous rationale, we hypothesized that aerobic training would blunt blood pressure increase induced by oral estrogen therapy in young post-menopausal women. Thus, the aim of this study is to compare the isolated and associated effects of aerobic training and oral estrogen therapy on ambulatory BP in young, hysterectomized, healthy, normotensive postmenopausal women.

2. Materials and methods

The participants were 45–60 years old, hysterectomized and at the post-menopausal period. They were nonsmokers, sedentary, and nonobese (body mass index $<30 \text{ kg/m}^2$). All subjects were normotensives, which were defined as the absence of antihypertensive medication use, an office BP lower than 140/90 mmHg [19]; and a 24-h BP lower than 130/80 mmHg [20]. In addition, none of the subjects had any chronic disease, as assessed by medical history, physical examination, standard hematologic and biochemical evaluation. Moreover, resting and exercise ECG were performed, and subjects who presented any abnormality indicating the presence of coronary heart disease, complex arrhythmias and/or left ventricular hypertrophy (Sokolow–Lyon index $>35 \text{ mm}$) were excluded. All women were absent of hormone therapy for at least three months before the study enrollment. Patients who did not fill these criteria were excluded.

This study took place at the General Hospital of the University of Sao Paulo, Brazil from July 2002 to July 2008, and during this period all the procedures were conducted by the same researchers with a standardized protocol. The procedures were carried out in accordance with the guidelines of the Helsinki Declaration on human experimentation and they were approved by Ethics Committee of the General Hospital of University of Sao Paulo. The subjects sign an informed consent prior to their participation. The study was registered in the Clinical Trials (NCT01120665) and followed the CONSORT Statements [21].

Many strategies were employed to compose the sample, including advertisements in local radio stations, newspapers, and public places on the university campus. Five hundred women volunteered for the study, and 440 did not meet the inclusion criteria. The sample was composed by sixty patients. They were randomly assigned according to a computer generated table of randomization list into four intervention groups: placebo and control (PLA-CO), estrogen therapy and control (ET-CO), placebo and aerobic training (PLA-AT) and estrogen therapy and aerobic training (ET-AT).

Hysterectomy was diagnosed by ultrasonography, and post-menopausal status was confirmed by amenorrhea for at least 12 months, associated with estradiol levels lower than 40 pg/ml, and serum luteinizing (LH) and follicle stimulating (FSH) hormones greater than 25 U/L and 35 U/L, respectively. Natural menopause was observed in 56 women and surgical menopause in four.

Randomization sequence was created using Stata 9.0 (StataCorp, College Station, TX) statistical software with allocation using random block sizes. The estrogen and placebo were in capsule form and identical in appearance. They were prepacked in boxes and consecutively numbered for each subject according to the randomization schedule. Each woman was assigned an order number and receives the capsules in the corresponding prepacked boxes. Subjects and investigators were double-blinded for the therapy used in both groups (placebo and estrogen therapy).

Estrogen therapy consisted of 1 mg/day of estradiol valerate, while placebo pills consisted of lactose powder, corn starch, microcrystalline cellulose, and magnesium stearate. The drugs' packages (therapy and placebo) were identical. At the beginning of the study, each participant received two boxes of 28 pills each, and was

instructed to take one pill per day at the same time every day. Appointments with physicians were scheduled every two months. At each appointment, two more boxes of pills were given, and adherence to the medication was assessed by counting the number of pills not taken during the preceding two-month period. The women who had taken less than 80% of the pills, were excluded from the study. At each visit, participants were submitted to a physical examination and body weight and blood pressure measurements.

Aerobic training was composed of cycling 3 days per week for 6 months. Exercise duration increased progressively throughout the training period from 20 to 60 min. Exercise intensity was established based on the maximal cardiopulmonary exercise test, by the heart rate obtained at the anaerobic threshold and at the respiratory compensation point, which corresponded to 56 ± 2 to $83 \pm 3\%$ of VO_2 peak. Adherence to the exercise program was addressed by a physical instructor who supervised all the exercise sessions. All women completed at least 85% of the training sessions. The control group was advised to maintain their normal habits, and not to begin any physical exercise program during the study period.

At the beginning and after six months, peak oxygen uptake (VO_2 peak) and ambulatory blood pressure were measured. A maximal cardiopulmonary exercise test was conducted in a climate controlled laboratory, on a cycle ergometer (Corival Cycle), employing a protocol with 30 W increments every three minutes until subjects were unable to go on. Before each test, a 12-lead ECG was obtained (Cardio Perfect ECG System MD, St. Paul, MN, USA). Before and during exercise, blood pressure was measured by auscultation, employing a mercury column sphygmomanometer, at the end of each stage. Heart rate and ECG were continuously monitored and were recorded every minute. Respiratory gases were collected and analyzed at each respiratory cycle (Medical Graphics Corporation (CPX/D System, St. Paul, MN, USA)) during all the tests. Peak oxygen uptake (VO_2 peak) was determined as the maximum value of oxygen consumption achieved during exercise in 30 s. Anaerobic threshold and respiratory compensation point were determined, respectively, by the lowest values of VE/VO_2 and VE/VCO_2 measured during the test [22]. These determinations were performed separately by three experts who were blinded to the group to which subjects belonged to. When there are disagreements in this first evaluation, the determination was made by a consensus.

Twenty-four hour ambulatory blood pressure monitoring was performed using an oscillometric device (Spacelabs 90207, Spacelabs Inc, Redmond, WA, USA). Measurements were taken in the non-dominant arm every 15 min during daytime (from 07.00 a.m. to 10.00 p.m.) and every 20 min at nighttime (from 10.00 p.m. to 07.00 a.m.). An appropriate cuff size was used for each patient's arm circumference. Device calibration was regularly checked by comparison with a mercury column. Mean BP values for 24-h, daytime and nighttime periods were calculated for analysis. In addition, nocturnal BP falls were also calculated in absolute (daytime BP–nighttime BP) and relative [absolute nocturnal BP fall/daytime BP $\times 100$] values. The reproducibility of ambulatory BP parameters in our laboratory is significant for 24-h systolic and diastolic BP; daytime systolic and diastolic BP; and nighttime systolic and diastolic BP (intraclass correlation coefficients = 0.869, 0.931, 0.865, 0.930, 0.792, and 0.854, respectively, $P < 0.05$); and it was not significant for nocturnal systolic and diastolic BP falls (intraclass correlation coefficient = 0.169 and 0.525, respectively, $P > 0.05$).

Primary outcomes were changes in twenty-four hour, daytime and nighttime ambulatory blood pressure after 6 months of estrogen therapy, aerobic training isolated or associated. Adverse effects of medication were analyzed through blood analysis, evaluating serum sodium and potassium, coagulation time, and hepatic and renal functions, and any discomfort referred by subjects that are

related with a severe climacteric symptoms were considered as exclusion criteria.

2.1. Statistical analysis

Considering a power of 80%, an alpha error of 5%, and a standard deviation of 3 mmHg, the minimal sample size necessary to detect a difference of 4 mmHg ambulatory blood pressure was calculated to be five subjects in each experimental group.

Only data from the subjects who effectively completed the entire protocol were analyzed (per-protocol analysis) [23]. Data normality was checked by means of the Shapiro–Wilks test, using the statistical package SPSS for Windows (version 13.0, Chicago, IL, USA).

To compare the initial characteristics of the four groups, a one-way ANOVA was conducted. To evaluate the isolated and combined effects of therapy and training on BP, a three-way ANOVA for repeated measures was employed establishing therapy (PLA or ET) and training status (CO or AT) as the between main factors, and the study phase (pre or post) as the within main factor. Post hoc comparisons were made using the Newman–Keuls test. Values of $P < 0.05$ were considered statistically significant, and data are presented as means \pm standard error. The software package used for these analyses was STATISTICA (StatSoft Inc, Tulsa, OK).

3. Results

During the study, 12 women were excluded because of lack of follow-up and one because of exercise-induced asthma. Thus, 47 volunteers finished the study. Their distribution throughout the groups was: 12 in the PLA–CO, 14 in the ET–CO, 12 in the PLA–AT, and 09 in the ET–AT (Fig. 1).

At the beginning of the study, no significant difference was detected among the four groups in regard to age, anthropometric measurements, hemodynamic data, hormone levels, time since hysterectomy, and VO_2 peak (Table 1). Twenty nine women had estradiol levels lower than 13 pg/ml, which is the minimal concentration detected by the assay (09 in the PLA–CO; 10 in the ET–CO; 06 in the PLA–AT; and 04 in the ET–AT). All others (volunteers) had estradiol levels lower than 40 pg/ml, and that is the reason these data are not in Table 1.

After 6 months, a significant increase in VO_2 peak was observed only in the volunteers who participated in aerobic training groups (combined values, PLA–CO and ET–CO = -0.4 ± 1.1 vs PLA–AT and ET–AT = $+4.6 \pm 1.0$ ml kg^{-1} min^{-1} , $P = 0.0003$). Moreover, in all the volunteers who were assigned to the ET groups, serum estradiol levels raised above 40 pg/ml, reaching a mean level of 56.1 ± 6.6 pg/ml. In the ET groups, plasma FSH decreased significantly (marginal values, PLA–CO and PLA–ET = -0.19 ± 2.60 vs ET–CO and ET–AT = -18.65 ± 5.19 U/L, $P = 0.0009$), while plasma LH did not change. There was no change in serum sodium and potassium, in hematological data, and in the indices of hepatic and renal functions in either group during the study (Table 2).

The effects of the interventions on ambulatory BP are shown in Fig. 2. A significant interaction was detected between the factors therapy and study phase for systolic BP. Thus, estrogen therapy produced a significant increase in 24-h ($P = 0.009$), daytime ($P = 0.008$) and nighttime ($P = 0.005$) systolic BP, independently of the training status. Moreover, a significant interaction was also observed between the factors therapy and study phase for 24-h ($P = 0.016$) and nighttime ($P = 0.015$) diastolic BP, showing that estrogen therapy also increased these variables independently of exercise status. Nevertheless, for daytime diastolic BP, a significant ($P = 0.039$) interaction was observed among all the factors (training status, therapy and study phase). Thus, daytime diastolic blood pressure

increased significantly only in the ET–CO group, and this response was significantly different from those observed in the other groups.

A significant interaction was detected between the factors training status and study phase for nocturnal systolic BP fall analyzed in absolute ($P = 0.039$) as well as in relative ($P = 0.046$) values. Thus, regardless of the hormone therapy, nocturnal systolic BP fall decreased significantly in the AT groups and did not change in the CO groups. The analysis of nocturnal diastolic BP fall presented a significant interaction among all the factors (training status, therapy and study phase) when values were analyzed in absolute ($P = 0.002$) as well as in relative ($P = 0.005$) values. Nocturnal diastolic BP fall decreased significantly only in the ET–AT group, and this response was significantly different from those observed in the other groups.

No significant difference was found for 24-h ($P = 0.642$), daytime ($P = 0.734$) or nighttime ($P = 0.950$) heart rate in any of the groups.

4. Discussion

The novelty of the present study is the finding that aerobic training abolished daytime diastolic BP increase induced by estrogen therapy in young healthy, normotensive postmenopausal women.

The effects of estrogen therapy on ambulatory BP have been poorly studied. In the present study, oral estrogen therapy increased 24-h, daytime and nighttime systolic and diastolic BP. These results contradict some previous studies that observed a significant decrease [8] or no change [24] in ambulatory BP with estrogen therapy. The main differences between the present study and the others are that the present investigation was a randomized, double-blinded and placebo controlled study, which investigated the effects of oral estrogen therapy in healthy, hysterectomized and recently postmenopausal women. Some of the previous studies had methodological limitations, such as the absence of a control group [8], different kinds of hormone therapy, like a combination of estrogen and progesterone [25], and different kinds of administration as transdermally instead of the oral form [26]. It is known that the estrogen effects depend on therapy characteristics, such as hormone type, association or not with progesterone, and route of administration [4].

On the other hand, the present results are in accordance with those of previous studies that investigated the oral effects of estrogen therapy on clinic BP. Steiner et al. [12] verified an increase of clinic BP with this kind of therapy in recently postmenopausal women, and a decrease in older women, suggesting that oral estrogen therapy can increase BP particularly in the first decade of the postmenopausal period. Nevertheless, to our knowledge, this was the first study to verify that oral estrogen induced an increase of BP in recent postmenopausal women and that this effect can also be observed in ambulatory BP levels.

The mechanisms underlying the increase in BP induced by estrogen therapy have been linked to the first hepatic passage of oral estrogen. There are some evidences that oral estrogen administration has a stimulatory effect on the renin–angiotensin II–aldosterone system [27,28]. Estrogen increases the production of renin substrates by the liver, which are converted to angiotensin I in the kidneys and to angiotensin II in the lungs, producing vasoconstriction, aldosterone release, and might lead to an increase in BP [29]. Furthermore, estrogen can also activate the coagulation process. Estrogen has been demonstrated to increase levels of fragment 1 + 2, thrombin–antithrombin complex and fibrinopeptide A, and decrease fibrinogen and coagulation inhibitors, such as antithrombin and protein C inhibitor tissue factor [30]. These processes might also lead to an increase in BP.

In the present study, aerobic training did not decrease ambulatory BP. Although a previous meta-analysis about this issue

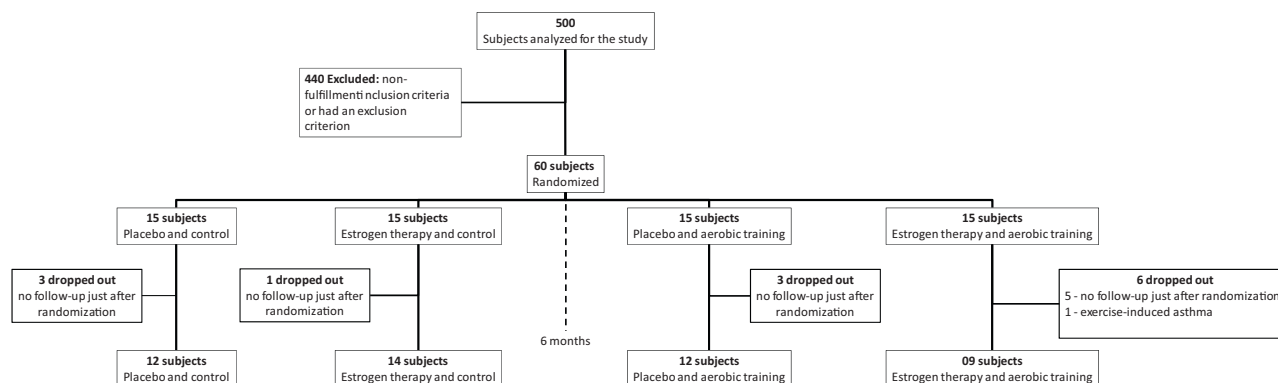


Fig. 1. Flowchart of entry and discontinuation of subjects during the study.

Table 1

Characteristics measured at the beginning of the study in the four study groups: placebo and control (PLA-CO), estrogen therapy and control (ET-CO), placebo and aerobic training (PLA-AT) and estrogen therapy and aerobic training (ET-AT).

	PLA-CO	ET-CO	PLA-AT	ET-AT	P-value
Age (year)	50 ± 1	52 ± 1	50 ± 1	51 ± 1	0.869
Weight (kg)	63.4 ± 2.7	64.7 ± 3.0	64.6 ± 2.4	66.7 ± 2.7	0.898
BMI (kg/m ²)	25.6 ± 0.8	25.5 ± 0.9	25.8 ± 0.7	27.1 ± 1.0	0.381
Clinic SBP (mmHg)	120 ± 2	119 ± 2	117 ± 3	121 ± 5	0.362
Clinic DBP (mmHg)	78 ± 2	71 ± 2	78 ± 2	77 ± 3	0.069
HR (bpm)	72 ± 4	69 ± 2	71 ± 3	66 ± 4	0.848
Ambulatory SBP					
24-h (mmHg)	115 ± 2	114 ± 2	117 ± 3	117 ± 3	0.786
Daytime (mmHg)	119 ± 2	117 ± 3	120 ± 3	121 ± 3	0.546
Nighttime (mmHg)	106 ± 2	104 ± 2	108 ± 3	103 ± 4	0.691
Ambulatory DBP					
24-h (mmHg)	72 ± 2	70 ± 2	76 ± 2	74 ± 3	0.793
Daytime (mmHg)	76 ± 2	72 ± 2	78 ± 2	78 ± 3	0.498
Nighttime (mmHg)	65 ± 2	61 ± 2	68 ± 2	62 ± 3	0.562
LH (U/L)	31.5 ± 3.6	40.9 ± 4.5	35.9 ± 4.8	33.8 ± 4.4	0.202
FSH (U/L)	71.8 ± 7.2	81.1 ± 9.2	75.6 ± 9.0	74.2 ± 9.2	0.515
Time since hysterectomy (year)	9 ± 2	9 ± 1	8 ± 2	6 ± 2	0.741
VO ₂ peak (ml kg ⁻¹ min ⁻¹)	18.5 ± 1.0	18.0 ± 1.0	20.4 ± 0.9	18.8 ± 1.3	0.831

BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate; LH – luteinizing hormone; FSH – follicle stimulating hormone; VO₂ peak – peak oxygen uptake.

Table 2

Changes (Δ) in plasma sodium and potassium, indices of hepatic and renal functions, and hematological data observed during the study in the four study groups: placebo and control (PLA-CO), estrogen therapy and control (ET-CO), placebo and aerobic training (PLA-AT) and estrogen therapy and aerobic training (ET-AT).

	PLA-CO	ET-CO	PLA-AT	ET-AT
Δ Sodium (mmol/L)	+2.1 ± 1.1	-0.4 ± 0.4	+0.5 ± 0.8	+0.6 ± 1.3
Δ Potassium (mmol/L)	-0.1 ± 0.2	-0.2 ± 0.1	+0.4 ± 0.4	+0.2 ± 0.2
Hepatic markers				
Δ TGO (U/L)	+1.1 ± 1.0	+1.6 ± 2.7	-2.2 ± 1.6	-1.6 ± 2.8
Δ TGP (U/L)	+1.5 ± 1.2	-1.1 ± 3.3	-5.9 ± 3.6	-3.6 ± 2.1
Renal markers				
Δ Urea (mg/dL)	-2.18 ± 2.81	-2.64 ± 1.75	-0.08 ± 1.46	-2.88 ± 2.02
Δ Creatinine (mg/dL)	-0.03 ± 0.03	-0.05 ± 0.03	-0.02 ± 0.02	+0.03 ± 0.03
Hematological data				
Δ TTPa (s)	-1.2 ± 1.1	-2.0 ± 1.8	-0.8 ± 1.2	-1.2 ± 0.8
Δ TP (%)	-0.2 ± 0.3	-1.3 ± 0.5	+0.4 ± 1.3	-0.4 ± 0.3
Δ TT (s)	+1.6 ± 1.2	-0.1 ± 2.0	+1.9 ± 1.0	-0.3 ± 0.5

Δ – difference between post and pre values; TGO – glutamic-oxaloacetic aminotransferase; TGP – glutamic-pyruvic aminotransferase; TTPa – activated partial thromboplastin time; TP – prothrombin time; TT – thrombin time.

reported a significant decrease of -3.3 (-5.8 to -0.9)/-3.5 (-5.2 to -1.9) mmHg in daytime systolic/diastolic BP, these reductions correlated with initial BP levels, being greater in hypertensive subjects [17]. Thus, as the women in the present study were normotensive, the absence of a decrease in ambulatory BP with aerobic training was already expected. In fact, many previous studies with normotensive subjects failed to show a signifi-

cant hypotensive effect of aerobic training on ambulatory BP [31,32].

Nevertheless, in the present study, aerobic training abolished ambulatory diastolic BP increase induced by estrogen therapy, what shows that when BP tended to increase, such as using estrogen, aerobic training prevented the increase. Even modest, the hypotensive effect of aerobic training, has clinical implications, once reductions

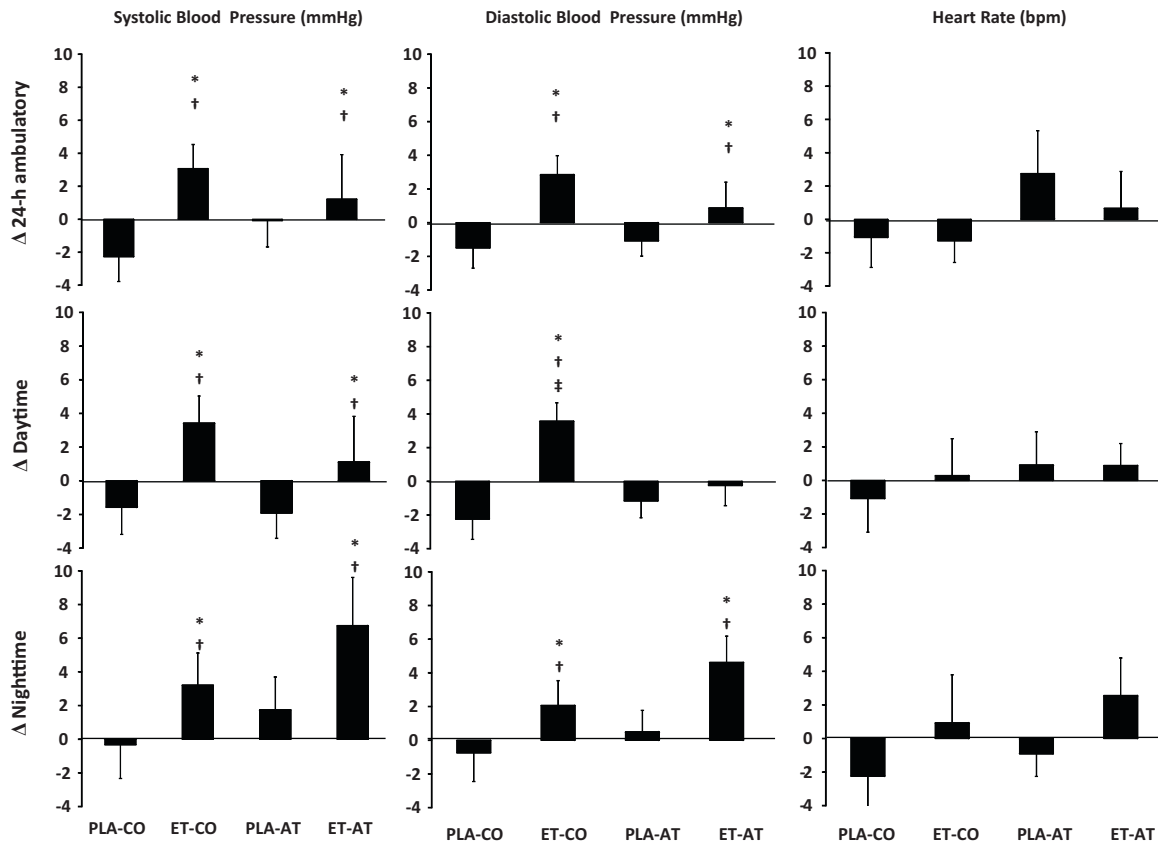


Fig. 2. Variations of difference between post and pre values (Δ) among the four groups to 24-h ambulatory, daytime, and nighttime systolic blood pressure, diastolic blood pressure, and heart rate. *Significantly different from pre values; †significantly different from placebo groups (PLA-CO and PLA-AT); ‡significantly different from estrogen therapy and aerobic training group (ET-AT); ($P < 0.05$).

of 2 mmHg on BP are associated with a 6% decrease in stroke mortality, and a 4% decrease in coronary artery disease [19]. Several factors may influence the BP reduction after aerobic training like the duration of the training program and the intensity of the exercise. In the present study, aerobic training was conducted for six months, three times a week, with moderate intensity and long duration. Seals et al. [18] observed a greater ambulatory BP reduction after 12 months of training compared to 6, so a longer training period could have had promoted a greater hypotensive effect. In regard of the exercise intensity, Marceau et al. [33] reported that moderate intensity training decreases daytime BP while more intense training decreases nighttime BP, what explains ours of daytime BP reduction since the intensity we used was moderate (50–70% of VO_2 peak). It is also important to emphasize that daytime BP decrease is clinically more relevant once BP levels are higher at this period [34].

As a consequence of reduced daytime BP, nocturnal diastolic BP fall decreased after the intervention in the ET-AT group. These results might seem odd at first, based on the fact that a decrease in nocturnal BP fall might represent an increase in cardiovascular risk [35]. However, it is noteworthy that this reduction was induced by a decrease in daytime diastolic BP and not by an increase in nighttime values. Thus, it is possible to think that training blunted the increase in BP produced by the awaken status, and this effect was especially evident when women were receiving estrogen therapy. It is important to state, however, that the reproducibility of nocturnal BP fall data is not good, as already shown in literature [36] and in our data. Thus, these results should be considered with caution.

Although estrogen-induced daytime diastolic BP increase was abolished by aerobic training, this effect was not significant for systolic daytime BP. Part of this result might be explained by sta-

tistical analysis, since the standard deviation was large for the ET-AT group. In fact, if analyses were performed separately for each group by *t*-test, daytime systolic BP would increase significantly in the ET-CO ($P = 0.028$) and would not change in the ET-AT group ($P = 0.622$). Thus, although not significant, aerobic training might also have had some hypotensive effect on estrogen-induced daytime systolic BP increase. This effect might be more evident over a longer period of training.

The mechanisms determining the effects of aerobic training in abolishing ambulatory BP increase induced by estrogen therapy are out of the scope of this study. However, previous studies suggest that hypotensive effects of aerobic training are mainly determined by decreasing peripheral vascular resistance [17]. In this regard, some studies reported that aerobic training reduces peripheral sympathetic nerve activity [17], and restores endothelium-dependent vasodilation by increasing the bioavailability of endothelial relaxing factors, such as nitric oxide, prostacyclin, prostaglandin E, and endothelium-hyperpolarizing factors [37]. Furthermore, aerobic training has been shown to have a direct decreasing effect on the activity of the angiotensin–renin system [38]; and emerging data suggest that aerobic training might improve fibrinolytic activity in postmenopausal women [39]. All these factors and the last two in particular, might have contributed to the counteracting effect of aerobic training on the increase in BP induced by oral estrogen therapy, especially for diastolic BP, which is more related to peripheral vascular resistance.

The clinical relevance of this study lies on the fact that we confirm that estrogen therapy increases clinical, and ambulatory BP, in young post-menopausal women, confirming the so-called “transient hypertensive effect of oral estrogen therapy”. However, we also demonstrated that aerobic training can help women avoid-

ing, at least in part, this hypertensive effect, since it abolished the increase in daytime BP induced by oral estrogen therapy. Thus, these results suggest that aerobic training might be recommended for young post-menopausal women who are going to begin estrogen therapy.

5. Conclusion

In conclusion, the present findings provide experimental support for the hypothesis that regular aerobic training is able to abolish, at least in part, the ambulatory BP increase induced by estrogen therapy in young, hysterectomized, healthy, normotensive post-menopausal women.

Contributors

Crivaldo Gomes Cardoso Jr. and Bruna Oneda performed throughout the study, participating from the selection of volunteers until the final production of the paper. Fabrício Collares Rosas and Eliana Labes, Gynecologist, participated in the selection of the volunteers and the completion of medical screening for the diagnosis of menopause. Sandra Balieiro Abrahão and Taís Tinucci contributed to the discussion of the effects of estrogen on ambulatory blood pressure in postmenopausal women. Decio Mion Jr. and Angela Maggio da Fonseca Co-Mentor of the study, supervised and coordinated the entire study. Cláudia Lúcia de Moraes Forjaz Mentor of the study, supervised and coordinated the entire study.

Competing interests

The authors report no conflicts of interest.

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