Low-dose estrogen therapy does not change postexercise hypotension, sympathetic nerve activity reduction, and vasodilation in healthy postmenopausal women

Bruna Oneda, Claudia L. M. Forjaz, Fernanda R. Bernardo, Tatiana G. Araújo, Josiane L. Gusmão, Eliana Labes, Sandra B. Abrahão, Decio Mion, Jr., Angela M. Fonseca and Tais Tinucci


You might find this additional info useful...

This article cites 70 articles, 30 of which you can access for free at:

[http://ajpheart.physiology.org/content/295/4/H1802.full#ref-list-1](http://ajpheart.physiology.org/content/295/4/H1802.full#ref-list-1)

Updated information and services including high resolution figures, can be found at:

[http://ajpheart.physiology.org/content/295/4/H1802.full](http://ajpheart.physiology.org/content/295/4/H1802.full)

Additional material and information about *American Journal of Physiology - Heart and Circulatory Physiology* can be found at:


This information is current as of December 15, 2012.
Low-dose estrogen therapy does not change postexercise hypotension, sympathetic nerve activity reduction, and vasodilation in healthy postmenopausal women

Bruna Oneda,1 Claudia L. M. Forjaz,2 Fernanda R. Bernardo,1 Tatiana G. Araújo,1 Josiane L. Gusmão,1 Eliana Labes,3 Sandra B. Abraão,1 Decio Mion Jr.,1 Angela M. Fonseca,3 and Tais Tinucci1,2

1Hypertension Unit, General Hospital, University of São Paulo; 2Exercise Hemodynamic Laboratory, School of Physical Education and Sport, University of São Paulo; and 3Gynecology and Climacteric Service, General Hospital, University of São Paulo, São Paulo, Brazil

Submitted 22 October 2007; accepted in final form 29 August 2008

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Address for reprint requests and other correspondence: T. Tinucci, Av. Prof. Mello Moraes, 65, Butantã, São Paulo, SP 05508-030, Brazil (e-mail: tinucci@usp.br).
known as postexercise hypotension and is considered clinically relevant (53). The results of various studies have suggested that a reduction in muscle sympathetic nerve activity (MSNA) is one of the mechanisms involved in postexercise hypotension in healthy individuals (3, 16, 23, 40), since it leads to a decrease in peripheral resistance. Other studies, however, have demonstrated no such sympatholysis after exercise (26–28).

Since estrogen might decrease sympathetic activity and increase blood flow, we hypothesized that estrogen therapy will potentiate the postexercise decrease in MSNA, as well as the postexercise increase in muscle blood flow, resulting in a greater postexercise hypotension. To our knowledge, the effect of estrogen therapy on postexercise hypotension has been studied only by Harvey et al. (30), who observed that estrogen therapy did not alter postexercise hypotension or vasodilation. However, the authors employed high-dose therapy (2 mg/day), the vasodilator effects of which have been shown to be less pronounced than those of treatment with lower doses (41). In addition, Harvey et al. (30) did not measure sympathetic activity. Therefore, the present study expands on previous findings, being designed to investigate the effect of low-dose estrogen on postexercise hypotension in healthy postmenopausal women. We also address the vascular and neural mechanisms involved in postexercise hypotension.

MATERIALS AND METHODS

Eighteen healthy, hysterectomized postmenopausal women (51 ± 1 yr) participated in this study. All gave written informed consent, and the study design was approved by the Ethics Committee of the General Hospital of the University of São Paulo (São Paulo, Brazil).

Of the 18 women evaluated, 15 had undergone natural menopause. In all 18 participants, the postmenopausal state was confirmed by determining the serum levels of follicle-stimulating hormone (>35 µIU/ml) and estradiol (<40 pg/ml). None of the women had received any hormone replacement therapy for at least 3 mo before the study outset, this being considered a sufficient amount of time for a complete washout to occur (15). All of the participants were nonsmokers, normotensive (blood pressure < 140/90 mmHg) and nonobese (body mass index < 30 kg/m²). Women with cardiovascular disease or any other chronic diseases were excluded, as were those in whom hormone replacement therapy was contraindicated. None of the women evaluated was engaged in any regular physical activity at the time.

The women were randomly divided into two groups: those allocated to receive estrogen therapy, consisting of 1 mg/day of estradiol valerate (estrogen group, ET, n = 9), and those allocated to receive placebo, consisting of 40 mg of lactose powder, 102 mg of cornstarch, 5 mg of microcrystalline cellulose, and 3 mg of magnesium stearate (placebo group, PLA, n = 9). These therapies were applied in a double-blinded manner. At the beginning of the study, each participant received two boxes of 28 pills each and was instructed to take one pill at the same time every day. Appointments with a physician were scheduled for once every 2 mo. At each appointment, two more boxes of pills were given, and adherence to the protocol was assessed by counting the number of pills not taken during the preceding 2-mo period. Women who took <80% of the pills were excluded from the study. At each visit, participants were submitted to a physical examination, a determination of body weight, and a measurement of blood pressure. Those presenting any adverse effects were automatically excluded from the study.

Experimental protocol. Tests were conducted and measurements were taken after 6 mo of administration, when the effects of the estrogen might already be present (5, 30, 36, 68, 69). Participants were familiarized with all of the experimental techniques before the execution of the tests and measurements.

For diagnostic purposes, brachial blood pressure was measured three times after 5 min of seated rest (7). All participants also underwent a maximal cardiopulmonary exercise testing. The test was conducted in a climate-controlled laboratory on a cycle ergometer (Corival Cycle) with a protocol of 30-W increases every 3 min. Oxygen uptake (VO₂) was measured directly during each respiratory cycle using a metabolic cart (CPX/D; Medical Graphics). Peak VO₂ was determined as the maximal value achieved during exercise (in ml·kg⁻¹·min⁻¹) in means of 30 s.

At least 7 days after the cardiopulmonary exercise testing, women were randomly assigned to participate in an exercise session (EX) and in a control session (CO) with an interval of at least 15 days between each session. In the CO, participants remained seated on a chair for 45 min. In the EX, participants exercised on the cycle ergometer for 45 min at 50% of VO₂ peak. The load necessary to achieve this intensity was calculated by determining the linear regression between load and the VO₂ recorded during the maximal cardiopulmonary exercise test. After each session, whether at exercise or rest, participants were placed in the supine position to rest for an additional 60 min, after which the measurements were taken. This was done to allow time for the MSNA assessment, as well as to maximize postexercise hypotension. All measurements were taken within a period of 10 min, during which the participants remained at rest.

Measurements. The MSNA was measured by microneurography (45), which measures sympathetic nerve activity in postganglionic type C fibers. For each participant, sympathetic nerve activity was recorded in a muscle fiber fascicle in the peroneal nerve, posterior to the fibular head. In brief, an active tungsten microelectrode (200 µm in diameter) was inserted into the muscle fiber fascicle, and a reference microelectrode was inserted subcutaneously at a distance of 1–3 cm from the active microelectrode. The recorded signal was fed to a preamplifier (gain, 1,000), an amplifier (variable gain, 40–60), and a bandpass filter (700–2,000 Hz), after which it was integrated (time constant, 0.1 s) to obtain a mean voltage display of the MSNA neurogram. Activity is expressed as burst frequency (in bursts/min).

During the experimental sessions, SBP, DBP, and mean blood pressure (MBP), as well as HR, were measured using an automated oscillometric device (DX-2710; Dixtal Biomédica, Manaus, Brazil) (44) attached to the calf of the participant. The calibration of the device was checked frequently by comparison with the mercury column.

Forearm blood flow (FBF, in ml·min⁻¹·100 ml⁻¹) was measured by venous occlusion plethysmography (62). In brief, an air-filled latex plethysmographic cuff was placed around the forearm and connected to a differential pressure transducer (R3800, Gold, Validyne). This arm was positioned above the right atrium to facilitate blood drainage. During measurements, the circulation to the hand was interrupted by a wrist cuff inflated to 200 mmHg, and a venous occlusion cuff was placed around the upper arm, then inflated to a subdiastolic pressure of 40–60 mmHg for 7 of every 15 s. This procedure interrupted venous return without affecting arterial inflow, which resulted in an increase in forearm volume, raising the pressure inside the plethysmographic cuff. The slope of increase in this pressure determined the FBF. Four measurements were taken every minute, and the FBF was measured over a 5-min period. The mean FBF value was calculated. Forearm vascular resistance (FVR, in units) was calculated by determining the ratio between MBP and FBF.

Statistical analysis. Data for both groups were collected in EX and CO. These data were compared using a two-way ANOVA, with one between main factor (ET or PLA groups) and one within main factor (CO or EX sessions). 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 ± SE. The sample size necessary to detect a decrease in SBP of at least 4 mmHg (SD 3), an
α-error of 0.05 and a β-error of 0.80, was calculated to be 9 participants.

RESULTS

The physical and cardiovascular characteristics, as well as hormonal status, at the end of the 6-mo period of treatment or placebo administration, are presented for both groups in Table 1. There were no significant differences between the groups in terms of any of the physical or cardiovascular variables evaluated, with the exception of estrogen levels, which, as expected, were significantly higher in the ET group than in the PLA group.

There were five women in the ET group and four women in the PLA group who initiated the experimental protocol with an exercise session. Exercise workloads were similar in the ET and PLA groups (35 ± 2 vs. 35 ± 1 W), and these workloads corresponded to similar intensities (50 ± 3 vs. 50 ± 4% of HR reserve).

The physiological responses observed in both groups and after control or exercise sessions are presented in Figs. 1 and 2. No significant interaction was observed between the factors of group and session for any variable. A significant effect of therapy was observed only for HR. Therefore, regardless of the group and session for any variable. A significant effect of therapy was observed only for HR. Therefore, regardless of the group and session for any variable.

In regard to the session factor, a significant effect was observed for all variables except HR. Therefore, regardless of the session type, 6 mo of oral estrogen administration had no effect on MSNA (33 ± 1 vs. 32 ± 2 burst/min, P = 0.9), SBP (152 ± 3 vs. 146 ± 3 mmHg, P = 0.3), DBP (75 ± 2 vs. 70 ± 2 mmHg, P = 0.3), MBP (93 ± 2 vs. 89 ± 2 mmHg, P = 0.4), FBF (2.7 ± 0.4 vs. 1.9 ± 0.3 ml·min⁻¹·100 ml⁻¹, P < 0.02), or FVR (37 ± 7 vs. 48 ± 9 units, P = 0.4), although it did result in a significant decrease in HR (59 ± 2 vs. 71 ± 2 beats/min, P < 0.01).

In regard to the session factor, a significant effect was observed for all variables except HR. Therefore, regardless of the group, a single session of aerobic exercise, compared with a CO, reduced SBP (145 ± 3 vs. 154 ± 3 mmHg, P < 0.01), DBP (71 ± 3 vs. 75 ± 2 mmHg, P = 0.02), MBP (89 ± 2 vs. 93 ± 2 mmHg, P = 0.02), MSNA (29 ± 2 vs. 35 ± 1 burst/min, P < 0.01), and FVR (33 ± 4 vs. 55 ± 10 units, P = 0.01), whereas it increased FBF (2.7 ± 0.4 vs. 1.6 ± 0.2 ml·min⁻¹·100 ml⁻¹, P = 0.02) and had no effect on HR (64 ± 2 vs. 65 ± 2 beats/min, P = 0.3).

DISCUSSION

The principal and novel finding of this study was that, in postmenopausal women, low-dose estrogen therapy did not change postexercise blood pressure, MSNA, or FBF responses. In addition, it decreased HR without changing its response after exercise. In general, low-dose estrogen therapy had no effect on postexercise physiological responses in healthy postmenopausal women. In fact, postexercise responses in the ET group were exactly the same as those observed in the PLA group, indicating that women receiving estrogen therapy and women not receiving such therapy can benefit equally from acute exercise.

To our knowledge, postexercise hypotension in postmenopausal women has been investigated in only one prior study (29), in which reductions of 5–10 mmHg in SBP and DBP were observed. These reductions are similar to those observed in the present study (9/4 mmHg), as well as to those reported in recent reviews on this issue (11, 22, 43, 53), which concluded that postexercise hypotension can be expected to produce reductions of 5–10 mmHg in SBP and DBP in normotensive individuals. Therefore, the degree of postexercise hypotension observed in healthy postmenopausal women is similar to that expected for the general normotensive population.

In the present study, postexercise hypotension was accompanied by an increase in FBF and a decrease in FVR, suggesting that it was mediated by the persistence of vasodilation after exercise. The reduction in peripheral vascular resistance after a single session of aerobic exercise has been previously reported in various populations (3, 13, 16, 21), including postmenopausal women (29). Many mechanisms have been proposed to explain this vasodilator response. Some authors suggest that it is mediated by the nitric oxide released due to shear stress during exercise (14, 34). However, Halliwill et al. (23) found no evidence to support the role of nitric oxide. Nevertheless, the same authors (22, 23) found that histamine might participate in postexercise hypotension via H1 and H2 receptors. Other mechanisms, such as thermoregulatory (19) and prostaglandin pathways (23, 25, 37), have been proposed but have yet to be confirmed. Other systemic vasodilators secreted during exercise, such as opioids, might also play some role (65). Our results suggest that the reduction in sympathetic activity might be an important mechanism. It is of note that FBF increased, although the exercise involved only the lower limbs. This underscores the possibility that systemic mechanisms, such as sympathetic decrease, opioid release, and thermoregulation, play a role. Since postexercise blood flow was measured in an inactive region and postexercise vasodilation is known to be more pronounced in exercised muscle (56), this response might have been even greater if the measurements had been taken on the leg.

The findings of the present study suggest that, at least under these experimental conditions, decreased MSNA might be involved in postexercise hypotension. There have also been studies in which no change in MSNA was observed after exercise (26–28). These discrepancies might be due to the differences in populations (healthy, hypertensive participants vs. postmenopausal women), exercise modalities (cycle ergometer vs. treadmill), or differences in experimental design (before and after vs. pre and post). Determining the mechanisms responsible for postexercise inhibition of MSNA is not

Table 1. Physical and cardiovascular characteristics, as well as hormone state, of the estrogen therapy and placebo groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Estrogen Therapy</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Age, yr</td>
<td>52±1</td>
<td>50±4</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>64±4</td>
<td>61±3</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.54±0.02</td>
<td>1.60±0.02</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26±2</td>
<td>25±1</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>121±5</td>
<td>121±12</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>73±3</td>
<td>75±7</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>76±4</td>
<td>73±7</td>
</tr>
<tr>
<td>Follicle-stimulating hormone, μg/ml</td>
<td>72±14</td>
<td>89±9</td>
</tr>
<tr>
<td>Estradiol, pg/ml</td>
<td>49±9*</td>
<td>14±2</td>
</tr>
<tr>
<td>Oxygen uptake peak, ml·kg⁻¹·min⁻¹</td>
<td>20.3±1.8</td>
<td>19.5±0.7</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, number of women. *P < 0.05, significant difference between groups.
within the scope of the present study, although previous studies (6, 9) have suggested that one such mechanism might be the resetting of the baroreflex operating point. Experimental studies (61) have indicated that prolonged stimulation of somatic afferents during exercise activates opioid and serotoninergic systems that centrally modulate baroreflex, inhibiting sympathetic outflow. In humans, Hara and Floras (27, 28) observed that endogenous opioid blockade changes postexercise baroreflex control of MSNA. It has also been proposed that postexercise sympathoinhibition is mediated by the facilitation of cardiopulmonary inhibitory reflexes (10).

Based on our results, we can say that healthy postmenopausal women present postexercise hypotension similarly to that seen in normotensive women and that this hypotension might be, at least in part, mediated by a decrease in muscle vascular resistance induced by a reduction in vascular sympathetic reduction.

Many previous studies have suggested that estrogen therapy has neural and cardiovascular effects under baseline conditions. Vongpatanasin et al. (68) found a 30% reduction in MSNA after estrogen administration. Some experimental studies have demonstrated an increase in vascular distensibility, as well as an increase in FBF, after estrogen administration (20, 42, 63). In addition, a number of studies have shown that estrogen therapy results in lower blood pressure (4, 5, 12). However, in the present study, estrogen therapy did not alter blood pressure, MSNA, blood flow, or vascular resistance. Nevertheless, our results are in accordance with those of other
studies (57, 60, 66, 68). The discrepancies might be explained by differences in the type or dose of estrogen administered. In the present study, estrogen administration decreased HR. This finding has already been reported in studies evaluating transdermal estrogen replacement therapy (47, 68) and high (2.5 mg/day) doses of estrone (31). Therefore, our results expand these effects for the use of low-dose hormone replacement therapy. In a recent study (51), physiological levels of estrogens were found to increase vagal modulation and decrease sympathetic modulation, which might explain the lower HRs observed after estrogen administration in the present study. This response might be associated with a reduction in cardiovascular risk, since a reduction in HR appears to have a favorable relationship with general and cardiovascular mortality rates (38). The observed reduction in HR, together with the lack of alterations in blood pressure, suggests that estrogen therapy increases stroke volume and/or systemic peripheral resistance. In the present study, FVR was not altered after estrogen administration, although other vascular beds might have been affected.

This study has limitations related to its experimental design. One major limitation is the fact that it employed oral estrogen therapy. The results might have been different if other routes of administration had been used or if progesterone had been included. In addition, the results are limited by the use of a low dose of hormone (1 mg/day). Future studies might involve different routes of administration, different treatment regimens, and varying doses. It should be borne in mind that the present study had a cross-population design and that longitudinal studies might provide better evidence to confirm our hypotheses. Another potential limitation is that the measurements were taken only after the interventions. This was done to avoid any problem related to performing the MSNA assessment four times in such a short period of time. Although comparisons between pre- and post-values might provide more information, the comparison between postsession values has been extensively employed (3, 9, 16–18, 24, 43, 58), and the results are considered reliable. Furthermore, to avoid any possible influence of the preintervention conditions, HR and blood pressure were measured at the beginning of each session, and the session was not allowed to commence unless the values were similar. Moreover, the sessions were randomly performed to avoid any learning effect (adaptation to experimental conditions). One final potential limitation is the fact that blood pressure was measured at the calf. The absolute values of SBP were expected to be ~30 mmHg higher in the calf than in the arm. This difference is well known and has been attributed to the summation of the incident wave with the reflected wave from the periphery (39). However, although SBP is higher at the calf, DBP and MBP values at the calf are similar to those observed for the arm (59). Since the measurements were obtained at the same site in every session and since the protocol analyzes blood pressure responses rather than absolute values, it is unlikely that the site of measurement influenced the results.

In conclusion, low-dose estrogen therapy did not alter the physiologial responses observed after a single session of aerobic exercise in healthy postmenopausal women. Women treated with estrogen and women receiving a placebo both presented postexercise reductions in SBP, DBP, MBP, MSNA, and peripheral vascular resistance, as well as an increase in blood flow. However, those treated with estrogen therapy presented lower HR values at baseline and after exercise.

ACKNOWLEDGMENTS
We gratefully acknowledge the work of the volunteers involved in this study, as well as the statistical contributions made by Isaac de Castro.

GRANTS
This study was supported by received financial support from the Fundação de Amparo à Pesquisa do Estado de São Paulo Grant 01/14989-7 and CAPES/DS/2005.

REFERENCES
Postexercise hypotension is mediated by reductions in sympathetic nerve activity. 

H1807

ESTROGEN AND POSTEXERCISE HYPOTENSION


41. Smolders RG, van der Mooren MJ, Kenemans P, van der Linden PW, Stehouwer CD, Sipkema P. 17β-Estradiol induces a rapid, endothelin-


