Estrogen replacement, vascular distensibility, and blood pressures in postmenopausal women

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De Meersman, Ronald E., Adrienne S. Zion, Elsa G. V. Giardina, J. Joseph P. Weir, James S. Lieberman, and John A. Downey. Estrogen replacement, vascular distensibility, and blood pressures in postmenopausal women. Am. J. Physiol. 274 (Heart Circ. Physiol. 43): H1539–H1544, 1998.—The pathogenesis of blood pressure (BP) rise in aging women remains unexplained, and one of the many incriminating factors may include abnormalities in arteriolar resistance vessels. The aim of this study was to determine the effects of unopposed estrogen on arteriolar distensibility, baroreceptor sensitivity (BRS), and hemodynamic parameters in postmenopausal women. Subjects gave their written informed consent, and the procedures were approved by the human research committee of Columbia University. All patients had been medically screened and were compliant with appropriate blood chemistry levels for FSH and estradiol for classification as postmenopausal and were compliant with menopausal status, respectively. In addition, blood samples were also analyzed for lipoproteins, which were considered an additional verification for treatment compliance. Of the 26 women who completed all phases of the study, only 8 met the appropriate blood chemistry levels for FSH and estradiol for classification as postmenopausal and were compliant with the treatment (Table 1). Data and analyses reported here refer to these eight subjects. Means ± SD for physical characteristics of the subjects were age 51.6 ± 6.3 yr, height 1.60 ± 0.06 m, weight 71.2 ± 14.9 kg, body mass index (BMI) 27.8 ± 6.0 kg/m², time since menopause 3.2 ± 3.1 yr. All subjects gave their written informed consent, and the procedures were approved by the human research committee of Columbia University. All patients had been medically screened and reported that they had been postmenopausal for at least 1 yr. The racial distribution of the eight subjects consisted of four Hispanics, three whites, and one African-American. None of the participants was hypertensive or taking any type of antihypertensive medications. After age and smoking, hypertension is the most critical risk factor in the prediction of cardiovascular diseases in women (23).

Therefore, the present study was designed to examine the effects of estrogen replacement therapy (ERT) on vascular distensibility, baroreceptor sensitivity (BRS), and hemodynamic parameters in postmenopausal women. These findings have clinical implications in the goals for treating cardiovascular risk factors in aging women. This phenomenon increases to one in three women who are older than 65 yr of age (23). Information based on 1991 data from the National Center for Health Statistics indicates that one-third of U.S. women 20–74 yr old have hypertension [systolic blood pressure (SBP) > 140 and diastolic blood pressure (DBP) > 90] or are taking antihypertensive medications. After age and smoking, hypertension is the most critical risk factor in the prediction of cardiovascular diseases in women (23).

The pathogenesis of hypertension remains unexplained in >95% of patients (24). A multitude of incriminating factors includes abnormality of the resistance vessels and loss of baroreceptor sensitivity. Epidemiological data support significant risk reductions in cardiovascular disease in postmenopausal women who receive estrogen replacement therapy (ERT; 6, 16, 20, 30). However, the modulating effects of estrogen or the lack of estrogen on arteriolar distensibility and baroreceptor sensitivity in postmenopausal women is largely unknown.

Therefore, the present study was designed to examine the effects of estrogen replacement therapy (ERT) on vascular distensibility, baroreceptor sensitivity (BRS), and hemodynamic parameters in postmenopausal women. These findings have clinical implications in the goals for treating cardiovascular risk factors in aging women.

baroreceptor sensitivity; blood pressure changes

CORONARY HEART DISEASE is the leading cause of death for women in the United States, responsible for one-quarter million deaths yearly (22). There appears to be a significant age dependency of coronary disease among women, such that one in nine women who are 45–65 yr of age has clinical evidence of coronary heart disease.

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Therefore, the present study was designed to examine the effects of estrogen replacement therapy (ERT) on vascular distensibility, baroreceptor sensitivity (BRS), and hemodynamic parameters in postmenopausal women. These findings have clinical implications in the goals for treating cardiovascular risk factors in aging women.
Estradiol, FSH, HDL, and LDL levels for all treatments

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<tr>
<td>Estradiol, pg/ml</td>
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<td>FSH, IU</td>
<td>75.2 ± 23.6</td>
<td>72.5 ± 23.2</td>
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</tr>
<tr>
<td>HDL, mg/dl</td>
<td>69.1 ± 13.7</td>
<td>65.4 ± 14</td>
<td>73.4 ± 13.9</td>
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<tr>
<td>LDL, mg/dl</td>
<td>130.4 ± 29.7</td>
<td>135 ± 33</td>
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Values are means ± SD. ERT, estrogen replacement therapy; FSH, follicle-stimulating hormone; HDL and LDL, high- and low-density lipoproteins, respectively.

of medication that would alter her blood pressure and autonomic physiology.

Study design. The subjects participated in a randomized crossover study with three identical experimental sessions. After the first session (baseline data collection), subjects were randomized to receive either conjugated equine estrogen (0.625 mg orally) or no drug for 1 mo. This design was instituted because subjects become unblinded due to physiological changes (i.e., fluid shifts or vasomotor and secretory changes) associated with estrogen administration. However, investigators and technicians performing data collections and analyses remained blind to all treatments. Each treatment was followed by a 4- to 6-wk washout period, and then patients were crossed over to the alternate treatment. Before each experimental session, a blood sample was obtained that was analyzed at a later date for FSH, estradiol, and lipoproteins.

Experimental protocol. The electrocardiogram (ECG) was recorded using a V5 lead configuration with an ECG machine (model 1511B, Hewlett-Packard, Waltham, MA). Respiration was measured from respiratory-induced temperature changes using a thermistor (YSI reusable temperature probe, Yellow Springs Instruments, Yellow Springs, OH) placed under the right nostril. Subjects were instructed to breathe through the nose throughout the data-collection protocols. Beat-by-beat blood pressure recordings from a finger cuff were made via a noninvasive photoplethysmographic device (Finapres, Ohmmeda, Englewood, CO). Blood pressure recordings were made with the left arm supported at heart (atrial) level. The position of the arm was maintained at the height of the heart for all three sessions. Validity and reliability of this photoplethysmographic device have been demonstrated against invasive methods, and it has been shown to provide accurate blood pressure changes when compared with intra-arterial blood pressures (28). All protocols allowed for normal breathing patterns as dictated by the strain of the protocol, with the exception of the exercising protocol, which allowed for the breathing pattern as dictated by the exercise protocol. Each protocol was designed to stimulate the sympathetic and/or parasympathetic branch of the autonomic nervous system. Initial measurements were obtained under resting conditions after a 15-min period of no activity during which a <5% fluctuation was present in heart rate (HR), blood pressure, and respiration. After the resting data collection phase, subjects performed a sustained isometric handgrip contraction using a cable tensiometer (model T51 Pacific Scientific, Anaheim, CA) for 1-min duration at 30% of the subject's previously determined maximal voluntary contraction. Prior experimentation in our laboratory indicated that a 1-min contraction was suitable for this population of middle-aged to older sedentary females. Valsalva maneuvers were then performed in which an expiratory pressure of 40 mmHg was maintained against a mercury manometer column (Medisco, Germany) for 15-s duration (12). Finally, a cycle ergometer (Bodyguard 9990, Oglaend, Norway) protocol was performed in which the subjects pedaled for 2 min at a workload that elicited HRs between 100 and 120 beats/min. This workload was recorded and repeated for the drug-free and ERT treatments. Except for the cycling, all protocols consisted of two trials. Resting times between trials and protocols were of sufficient duration to allow the subject's HR and blood pressure to return to pretesting values in which HR, SBP, and DBP varied by <5% for at least 1 min.

Data acquisition and analyses. The ECG, blood pressure, and respiratory analog signals were fed to a 586 Dell computer (Dell, Austin, TX) and digitized via an analog-to-digital conversion board (ATM10-16X, National Instruments, Austin, TX) at 200 samples/s (Hz). The data acquisition and postacquisition analyses were performed with programs written with LabView software (National Instruments). The digitized ECG, blood pressure, and respiratory data were analyzed for the determinations of heart period variability, arteriolar distensibility, baroreceptor sensitivity, and blood pressure changes as described below. All files were analyzed by one technician. In addition, one-third of all files, selected randomly, was analyzed by another technician, and results were compared. Percent agreement between the two independent analyses will be reported for all dependent variables.

Arteriolar distensibility. Arteriolar distensibility, an index of arteriolar stiffness, was assessed for the resting protocol. The determinations were made using a program that calculated the area under the dicrotic notch (8, 15). The area boundaries were delineated interactively. Specifically, the boundaries in the pulse wave were set at the nadir of the incisura of the dicrotic notch and at the diastolic trough. The area defined by these boundaries was then integrated. The segment of analysis was an identical epoch of ~10 pulses for all subjects and contained an inspiratory and expiratory phase. This standardization procedure was considered necessary to accommodate the cyclical variations in the dicrotic notch area during breathing (9). The dicrotic notch areas were then normalized by relating it to the corresponding pulse pressure [normalized units (NU)], with the resulting variable termed the distensibility index. Agreement of the independent analyses between different technicians for arteriolar distensibility was 97.2%.

Autonomic analyses. Power spectral analysis of heart period variability was used to assess cardiac autonomic nervous system function. After inspection of the ECG, R-wave peaks and interbeat intervals (IBIs) were determined. The sequence of the interbeat intervals was fitted with a rectangular interpolation procedure to provide a continuous data stream. For each data segment, a power density spectrum was created via a discrete Fourier transform of the interpolated IBI data. The resulting power density spectrum was integrated and areas associated with discrete frequency bands were determined. Power spectra within the 0.07- to 0.15-Hz range were defined as low-frequency (LF) components, whereas those at the frequency of 0.15–0.4 Hz were defined as the high-frequency (HF) components. The ratio of LF to HF power was also assessed in this study because this ratio has been reported to provide information about sympathovagal balance (25). These autonomic analyses were carried out for the resting protocol. Agreement between the two independent analyses for LF, HF, and sympathovagal balance was 100%.

Baroreceptor sensitivity. Baroreceptor sensitivity was assessed by recording cardiac deceleration (reflex bradycardia) in response to a Valsalva-induced increase in SBP. The R-R intervals were plotted against the preceding systolic arterial pressure, and a linear regression analysis was performed.

Table 1. Estradiol, FSH, HDL, and LDL levels for all treatments

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Values are means ± SD. ERT, estrogen replacement therapy; FSH, follicle-stimulating hormone; HDL and LDL, high- and low-density lipoproteins, respectively.
for those points included between the beginning and the end of the first significant increase in systolic arterial pressure. The baroreceptor sensitivity index (BRSI) was expressed as the slope of the linear regression relating SBP and the cardiac cycle length. Validity and reliability of this method have been established previously (12). Agreement between the two independent analyses of BRSI was 96%.

Hemodynamics. For the resting and the isometric exercise protocols, the HR, SBP, and DBP were determined. In addition, rate-pressure product ([RPP = (SBP × HR)/1,000]) was then calculated. Estimates of stroke volume (SV) were obtained for the resting protocol. This measurement was derived from the beat-by-beat pulse wave. Specifically, the area under the systolic wave or flow velocity integral was interatively delineated and integrated, which parallels SV (27). This area measurement was then entered in a gender-specific regression equation and provided an estimate of the subject's SV. The validity and reliability of this measurement at rest have been reported previously (3). As with the measurement ofarteriolar distensibility, the HRs, SBPs, DBPs, and calculated RPPs were determined from identically occurring time windows within the data-collection epoch. All measurements included an entire breathing cycle (inhalation and exhalation). Agreement between independent analyses for HRs, SBPs, DBPs, and RPP was 96%.

For all dependent variables, the data were analyzed using a three × four repeated-measures analysis of variance (ANOVA) (3 treatments: baseline, drug-free, and estrogen; 4 protocols: rest, isometric, Valsalva, and exercise). Significant effects were further analyzed with Newman-Keuls post hoc tests. An α level of 0.05 was considered significant for all analyses.

RESULTS

Arteriolar distensibility. Arteriolar distensibility, an index of arteriolar stiffness, determined for the resting protocol revealed a significant difference after ERT (4.9 ± 1.3 NU) compared with baseline (3.5 ± 1.4 NU) (P < 0.05). Specifically, the distensibility showed significant augmentation after ERT, suggesting a decrease in arteriolar stiffness (Table 2).

Sympathovagal balance. For the resting protocol, the repeated-measures ANOVA showed a trend (P = 0.061) toward a lower sympathovagal balance after ERT, albeit this trend failed to reach statistical significance compared with the baseline and drug-free treatments. Similarly, a trend toward parasympathetic augmentation (P = 0.06) and a concomitant downward trend in sympathetic outflow (P = 0.08) were noted after ERT. However, neither of these trends reached statistical significance compared with the other treatments. No significant differences or trends in sympathovagal balance were observed for any of the other protocols (isometric and dynamic exercise).

Baroreceptor sensitivity. The repeated-measures ANOVA revealed significant differences (P < 0.05) in baroreceptor sensitivity between treatments. Post hoc analyses revealed significantly higher baroreceptor sensitivities after ERT (4.8 ± 0.9 mmHg/ms) compared with baseline (2.6 ± 0.6 mmHg/ms) and drug-free (2.2 ± 1.8 ms/mmHg) treatment (Table 2).

Hemodynamic variables. Significant differences were noted for HRs during the isometric contraction after ERT (75.5 ± 2.9 beats/min) compared with baseline (81.7 ± 8.4 beats/min) and drug-free (83.6 ± 7.8 beats/min) treatments (P < 0.02). No significant differences were noted in resting HRs between ERT and the other treatments. The resting and isometric exercise protocols showed significantly lower SBP and DBP after ERT (P < 0.05) (Table 3). Significance was achieved in RPP between estrogen and the alternate treatments for the isometric protocol (P < 0.05). No significant differences in pulse pressures were noted between any of the treatments at rest; however, a trend toward lower pulse pressures after ERT was noted during the isometric contraction (P = 0.058) (Table 4). No significant differences in SVs were noted for any of the protocols.

Table 3. Systolic and diastolic blood pressure changes from baseline after drug-free treatment and ERT for subjects at rest and during isometric exercise

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rest</th>
<th>Isometric Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔSBPp</td>
<td>-2</td>
<td>-1.7</td>
</tr>
<tr>
<td>ΔDBPp</td>
<td>-2.7</td>
<td>-0.2</td>
</tr>
<tr>
<td>ΔSBPd</td>
<td>-9.6</td>
<td>-6.3*</td>
</tr>
<tr>
<td>ΔDBPd</td>
<td>-5.7*</td>
<td>-8.4*</td>
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ΔSBPp and ΔDBPp, systolic and diastolic blood pressure changes from baseline after drug-free treatment, respectively; ΔSBPd and ΔDBPd, systolic and diastolic blood pressure changes from baseline after ERT, respectively. *Significantly different from baseline (P < 0.05).

Table 4. Finger arteriolar systolic, diastolic, and pulse pressures for three treatments while subjects were at rest and during isometric exercise

<table>
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<th>Treatment</th>
<th>Baseline</th>
<th>Drug free</th>
<th>ERT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>111 ± 15.2</td>
<td>109 ± 13.1</td>
<td>102 ± 12.5*</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>70 ± 11.4</td>
<td>68 ± 9.9</td>
<td>64 ± 10.8*</td>
</tr>
<tr>
<td>Pulse pressure, mmHg</td>
<td>41 ± 14.5</td>
<td>41 ± 13.2</td>
<td>38 ± 13</td>
</tr>
<tr>
<td>Isometric exercise</td>
<td></td>
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</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>136 ± 21.3</td>
<td>135 ± 28.5</td>
<td>117 ± 15.9*</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>80 ± 11.3</td>
<td>78 ± 10.2</td>
<td>70 ± 8.4*</td>
</tr>
<tr>
<td>Pulse pressure, mmHg</td>
<td>56 ± 23.2</td>
<td>57 ± 25.4</td>
<td>47 ± 15.6</td>
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</table>

Values are means ± SD. *Significantly different from other treatments (P < 0.05).
Blood pressures. All blood pressure recordings were made in the middle phalanx of the middle finger (peripheral resistance vessel). Pressure gradients along the vascular tree cause finger pressures to differ from the mean brachial pressure (26). This in turn would lead to different pressures from normative (brachial) systolic and diastolic pressures. Therefore, our intent is to report the changes rather than absolute pressures. Accurate changes with the use of the Finapres have been previously reported in comparison with intraarterial measurements (26). In addition, blood pressure responses to circulatory stimuli in the finger arterioles are similar in appearance and direction but less so in magnitude compared with brachial blood pressure responses (26). Blood pressures were recorded throughout the resting period via a beat-by-beat blood pressure recorder. Average blood pressures were obtained from at least 10 individual blood pressures of stationary (~<3% fluctuation) data. This has been suggested as an optimal number of blood pressure readings needed to obtain representative blood pressures (21). In addition, this segment included a complete breathing cycle (inhalaion and exhalation) to account for the blood pressure oscillations during breathing (9).

Verification of compliance to treatment. The eight subjects who met all postmenopausal criteria had a mean FSH level of >40 international units (IU), and mean estradiol blood levels after ERT were 69 pg/ml. To further verify subject compliance, we analyzed blood samples for high-density (HDLs) and low-density lipoproteins (LDLs). Increases in HDLs and decreases in LDLs (changes ranged from 6 to 18%) were noted after ERT compared with baseline or drug-free treatments (P < 0.05) (Table 1). The overall compliance for this study was 30%, which appears to be considerably above average because prior research has indicated poor compliance (14%) with this treatment (18).

DISCUSSION

The present results, obtained in postmenopausal women using noninvasive techniques, demonstrate that ERT improves resistance vessel distensibility and baroreceptor sensitivity. In addition, ERT lowers blood pressures and RPP, at rest and during a physiological challenge. These changes represent a mechanism of adaptation in which cardiovascular risk factors may be significantly reduced. Most of the epidemiological ERT studies report significant reductions in cardiovascular mortality risk in postmenopausal women via favorable effects of estrogens on serum lipid profile (1, 6, 16, 29). However, the significant age-dependent rise of coronary heart disease among women 45–65 yr old appears to be due to a multitude of nonautonomic and autonomic factors, many of which require further study (13, 29). Therefore, within this mosaic, we decided to explore the effects of estrogens on a nonautonomic modulator, arteriolar distensibility, and several autonomic reflexes, including baroreceptor sensitivity and efferent autonomic outflow. Additionally, we studied the effects of ERT on arteriolar blood pressures and RPP. Prior animal studies provide evidence of a direct, receptor-mediated vasodilatory effect of estrogens on female baboon myocardium and aorta (2, 10, 19). To further explain the effects of this improved arteriolar distensibility as a result of ERT on cardiovascular risk factors, we studied baroreceptor sensitivity and efferent autonomic outflow and how these mechanisms affect arteriolar blood pressures and RPP, a noninvasive marker of myocardial oxygen consumption (MVo2) (Fig. 1).

All components of this model were tested using standard autonomic tests. These provocations mimicked real-life events (rest, short-term isometric contraction, and short-term dynamic exercise), and the related significant findings will be discussed. Arterioles are distensible and consequently are able to dampen the pulsatile systolic output of the ventricles (24, 33). This characteristic buffering function is due to the viscoelastic properties of the arteriolar wall. The results in our investigation strongly suggest an improvement in viscoelastic properties of the arteriolar wall after ERT, an observation that has been made in prior animal model studies (2).

To explain the clinical implications of improved arteriolar distensibility after ERT, we evaluated some of the components modulating arteriolar blood pressure. Blood pressure is the product of cardiac output (Q) and peripheral vascular resistance (PVR). With this model, blood pressure is governed by the product of Q (volume) and PVR (constriction and/or dilation). Therefore, any alteration in one or both of these parameters will translate into an alteration in blood pressure. Our analyses failed to reveal any differences in the estimates of SV at rest and between any of the treatments. Hence, these findings strongly suggest that no cardiac output (Q = HR × SV) differences were present after ERT compared with the other treatments.

A frequent by-product of ERT appears to be weight gain, primarily due to the fluid-retention properties of estrogen. This volume change could augment cardiac output. However, we did not observe any significant changes in BMI of our subjects between any of the treatments. Perhaps the treatment period (1 mo) in this investigation was too short for significant weight...
changes to occur. Therefore the central (Q) or volume component of the equation did not seem to be affected by ERT. The remaining component of the equation (PVR) was then studied. Prior observations indicate that the autonomic nervous system extensively regulates muscular tone of the arterioles (5). Our results support this observation because improvements in arteriolar distensibility were observed while subjects were on ERT. This could partly explain the reduction in pressures via a change in arteriolar vasodilatory properties (distensibility) that was observed with ERT. To further explain these favorable changes, we evaluated a key component of the autonomic reflex pathway, namely, baroreceptor sensitivity. The baroreceptors provide a constant surveillance and a buffering response to blood pressure oscillations. Clinically, according to Sowers and Mohanty (32), loss of baroreceptor sensitivity constitutes a major cardiovascular risk factor (32). Our findings provide strong evidence that ERT plays a favorable role in the modulation of baroreceptor sensitivity. The enhanced baroreceptor sensitivity after ERT emerged quickly; statistical significance (P < 0.05) was reached with a relatively small number of subjects completing all trials (34). This observation that baroreceptor sensitivity is a sensitive marker and major contributor to vagal-cardiac activity has recently been described by Davy et al. (7). Integrated baroreflex responses modulate afferent and efferent autonomic outflow and are tethered to viscoelastic properties in the arterial wall (11). These properties of enhanced arteriolar distensibility and baroreceptor sensitivity after ERT help to explain the favorable, albeit statistically insignificant (P = 0.08), trend in sympathovagal balance. These influences provide further evidence on the interrelationships of arteriolar blood pressures as depicted in our proposed model.

RPPs were significantly lower for isometric exercise after ERT treatment. Previous work has demonstrated that changes in the product of HR and blood pressure are associated with parallel changes in $\text{MV}_2$ and myocardial blood flow in a variety of circumstances (14). The observation of significantly lower RPPs would imply a lowering of cardiac work (MV$\text{O}_2$) with ERT.

The above findings at rest and during isometric exercise are of substantial clinical importance because arteriolar stiffness, baroreceptor sensitivity, and blood pressures have been shown to play an etiologic role in the development of a major cardiovascular risk factor: hypertension (4, 15, 17). Furthermore, in terms of cardiovascular morbidity and mortality, the PVR- or constrictive-hypertensive individual has a significantly more ominous prognosis compared with the Q or volume hypertensive (17). In addition, an overactivity of the sympathetic nervous system has been implicated as one of the pathogenetic factors in hypertension (24). Therefore, it appears from our findings that ERT plays a significant role in altering the PVR component of the blood pressure equation. Noting that, after age and smoking, hypertension is considered the most critical risk factor in women (22), our observations provide strong support for the cardioprotective effects of ERT via enhanced arteriolar distensibility and baroreceptor sensitivity. The influence of menopause on blood pressure is surrounded with controversy. Specifically, no rise in blood pressure with menopause was observed in the Framingham study (13). In contrast, higher blood pressures were reported in a cross-sectional study by Staessen et al. (29). Use of contraceptive pills (synthetic estrogens) has been occasionally associated with an increase in blood pressure (29). Our longitudinal findings revealed significant reductions in systolic and diastolic blood pressures after ERT treatment compared with baseline and drug-free treatments. These observations were corroborated in a prior investigation in our laboratory (34).

In conclusion, the present study has demonstrated that ERT modulates resistance vessels, baroreceptor sensitivity, and blood pressures in postmenopausal women. Our findings provide evidence that short-term administration of estrogens may have beneficial effects on cardiovascular hemodynamics by lowering blood pressure and RPP. These findings have important clinical implications in the goal for treating cardiovascular risk factors in aging women, a population at high risk for cardiovascular morbidity and mortality.

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