Menopausal Status Influences Ambulatory Blood Pressure Levels and Blood Pressure Changes During Mental Stress

Jane F. Owens, DrPH; Catherine M. Stoney, PhD; Karen A. Matthews, PhD

**Background.** Frequent and large cardiovascular and neuroendocrine responses to psychological stress are thought to enhance an individual’s risk for cardiovascular diseases. Preliminary data suggest that levels of reproductive hormones affect the magnitude of stress responses, perhaps contributing to the protective effect of ovarian hormones on premenopausal women’s rates of coronary heart disease.

**Methods and Results.** Healthy middle-aged men and premenopausal and postmenopausal women performed a series of standardized mental and physical challenges while blood pressure, heart rate, plasma catecholamines, lipids, and lipoproteins were measured. Subjects then wore an ambulatory blood pressure monitor during two consecutive workdays. Results showed that postmenopausal women had larger mean±SEM stress-induced increases in systolic blood pressure (24.7±2.2 mm Hg) and diastolic blood pressure (14.3±1.0 mm Hg) compared with either premenopausal women (16.9±1.3 and 10.2±0.9 mm Hg) or men (17.7±1.5 and 10.9±1.1 mm Hg, respectively). Postmenopausal women and men had higher mean±SEM ambulatory diastolic blood pressure levels (75.5±3.2 and 76.4±1.8 mm Hg) than did premenopausal women (69.9±2.2 mm Hg). Large blood pressure responses during public speaking were associated with high cholesterol levels and low educational attainment.

**Conclusions.** Menopause is associated with enhanced stress-induced cardiovascular responses and elevated ambulatory blood pressure during the workday. These effects may contribute to the risk of cardiovascular morbidity and mortality after the menopause. (Circulation. 1993;88:2794-2802.)

**Key Words** • risk factors • women • catecholamines • blood pressure

Sex differences in rates of coronary heart disease (CHD) morbidity and mortality are largest in magnitude before the menopause. Furthermore, postmenopausal women have higher rates of CHD than do premenopausal women, especially among those who have a surgical menopause relatively early in life. Observational studies show that ever or current users of estrogen replacement therapy have lower rates of CHD than never users. These types of data have led investigators to assume that ovarian hormones, especially estrogens, protect women from CHD in midlife and that their relative absence after the menopause contributes to accelerated rates of CHD in the later years.

The mechanisms accounting for the protective influence of estrogen are partially known. Perhaps best established is that estrogen influences lipid metabolism, resulting in women having a more favorable lipid profile than men. Estimates are that about 25% to 50% of the beneficial effects of estrogen replacement therapy on women’s rates of CHD are due to favorable lipid metabolism.

Another potential contributor to the development of CHD is frequent and large cardiovascular and neuroendocrine responses to mental or psychological stress. It is speculated that exaggerated responses to stress may cause arterial injury as a result of hemodynamic forces such as turbulence and shear stress. Such injury can result in increased endothelial permeability to plasma lipoproteins, release of mitogenic substances by newly regenerated endothelial cells, subsequent proliferation of intimal smooth muscle cells, and a disruption of the lipid metabolism of endothelial cells. It is also likely that large cardiovascular or neuroendocrine responses to acute mental stress may trigger clinical events in individuals with subclinical or clinical disease through hemodynamic, vasoconstrictive, or coagulation factors.

Cardiovascular and neuroendocrine responses to mental stress may be influenced by reproductive hormone status. Supportive of the latter are data indicating that pregnant women have diminished blood pressure responses to mental stress compared with their prepregnancy responses or to nonpregnant control subjects; sex differences in cardiovascular responses to mental stress emerge at adolescence and remain in adulthood; and, in one study, postmenopausal women have larger increases in heart rate, systolic blood pressure, and plasma epinephrine during public speaking than their age-matched premenopausal counterparts. No study has directly compared the cardiovascular and neuroendocrine responses to mental stress of premenopausal and postmenopausal women and men. On the basis of previous data and the presumed protective effects of estrogens on cardiovascular and neuroendocrine re-

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From the Department of Psychiatry, University of Pittsburgh School of Medicine (J.F.O., K.A.M.), and the Miriam Hospital, Brown University, Providence, RI (C.M.S.).
Reprint requests to Dr Jane Owens, Department of Psychiatry, University of Pittsburgh, 3811 O’Hara St, Pittsburgh, PA 15213.
responses to mental stress, the present study tested the hypotheses that postmenopausal women would exhibit larger responses to mental stress than would premenopausal women and that postmenopausal women would exhibit stress responses similar to or smaller than those of men.

Since individuals who exhibit large blood pressure changes to mental stress presented in the laboratory often do not have elevated ambulatory blood pressure levels,12,13 the validity of using laboratory indices to extrapolate to physiological responses in the natural setting has been questioned. Furthermore, ambulatory blood pressure studies have largely ignored the potential effect that reproductive hormones might have in determining cardiovascular responses to daily life situations, since they failed to partition participants according to hormonal profiles. A second purpose of the study was to evaluate whether postmenopausal women and men have elevated ambulatory blood pressure levels associated with the stresses of daily living compared with premenopausal women, taking into account resting blood pressure level, body mass index (BMI), and age.

There is evidence that sympathetic nervous system activation during psychological stress can alter lipid and lipoprotein levels.14 If so, those individuals who characteristically show elevated cardiovascular and neuroendocrine responses during stress should also show elevations in lipid and lipoprotein levels. Indeed, among men with cardiovascular disease, large cardiovascular responses to mental stress were associated with elevated lipid and lipoprotein levels.15,16 Similar results were reported by Suarez and colleagues17 in type A and high-hostile men. However, none of these studies controlled for weight or BMI, which may be correlated with psychological stress and is correlated with lipid levels. A third objective of our study was to evaluate the relation between cardiovascular reactivity to mental stress and levels of lipids and lipoproteins and educational attainment, taking BMI into account.

**Methods**

**Subjects**

Participants were 15 male and 34 female healthy, middle-aged (age, 40 to 55 years) volunteers recruited through an advertisement. Subjects were all employed for pay outside the home and were primarily from a university community. Subjects were nonsmokers, normotensive, normocholesteremic, free from chronic disease, <20% overweight, and were not taking any medications known to influence the cardiovascular system. Women with a history of gynecologic cancer or who were taking hormone replacement therapy were excluded. Women were categorized as premenopausal if they reported having regular menstrual cycles for the 6 months immediately before their participation in the study and as postmenopausal if they reported no menses for at least 6 months before study. In addition, menopausal status was confirmed by laboratory analysis of levels of estradiol, progesterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH). Reproductive hormones were measured in the female participants. Of the 34 women, 17 had hormone profiles consistent with premenopausal status, and 16 had profiles indicating that they were postmenopausal. One woman was perimenopausal, and her data were excluded from the analysis. No effort was made to schedule the premenopausal women according to their menstrual cycle phase because no consistent effect of menstrual cycle phase on cardiovascular or neuroendocrine responses has been demonstrated in young adult women.18

**Measurement of Physiological Parameters**

Disposable silver-silver chloride electrodes were placed in a modified lead II configuration on the chest. The ECG signal was filtered through a Grass model 7B polygraph (model 7P4D preamplifier), and R waves were detected electronically. Interbeat intervals in milliseconds were calculated from the R wave of the signal. Heart rate calculated from the interbeat interval was then simultaneously displayed and stored on an IBM-AT.

Blood pressure was measured automatically by an IBS model SD700-A automated blood pressure device (Industrial & Biomedical Sensors Corp). Cuff inflation levels and deflation rates were individually determined according to blood pressure and heart rate levels at baseline. Before data collection was initiated, blood pressure measurements were taken via the IBS and by a standard mercury manometer to ensure that the automated blood pressures were accurate. The two blood pressure measurements were always within 4 mm Hg of each other. Pearson correlation coefficients between the two measures in another sample of 179 middle-aged men and women studied by us were .97 for systolic blood pressure and .89 for diastolic blood pressure. Voltages associated with systolic blood pressure and diastolic blood pressure were passed through a 12-bit analog-to-digital converter (Metabyte), then displayed and stored on the IBM-AT.

Blood samples were collected via syringe through thromboreistant 19-gauge catheters that were pretreated with sodium heparin, and plasma was obtained by centrifugation of whole blood in a Damon refrigerated centrifuge (model CRU-5000) immediately after collection. Serum was extracted by centrifugation, and both plasma and serum were stored at −90°C in a Revco freezer (model ULT-790). Hematocrit tubes were spun in a hematocrit centrifuge (International Equipment Co) according to the Guest centrifuge method and read with a Reading Chart (A.H. Thomas Co).

Progesterone, estradiol, and LH were determined from serum with a solid-phase radioimmunoassay method (Diagnostic Products Corp). This method is highly specific and demonstrates little cross-reactivity to related compounds that might be present in samples. A similar radioimmunoassay procedure was used to determine FSH levels from serum (Clinical Assay Corp). Catecholamines were determined from plasma by high-performance liquid chromatography with electrochemical detection and an alumina extraction procedure.19 Laboratory intra-assay coefficients of variation were 13.4% for epinephrine and 2.5% for norepinephrine.

Serum lipids and lipoproteins were analyzed in the Heinz Laboratory of the Graduate School of Public Health, a laboratory certified by the Centers for Disease Control and Prevention/National Heart, Lung, and Blood Institute Cholesterol Standardization Program. Duplicate determinations are obtained to ensure precision. Triglyc-
erides and total cholesterol were determined enzymatically.\textsuperscript{20,21} High-density lipoprotein cholesterol (HDL-C) and high-density lipoprotein-3 (HDL\textsubscript{3}-C) were assayed by the dextran precipitation technique. Low-density lipoprotein cholesterol (LDL-C) was arithmetically determined from the Friedewald equation.\textsuperscript{23} High-density lipoprotein cholesterol-2 (HDL\textsubscript{2}-C) was calculated as the arithmetic difference between HDL-C and HDL\textsubscript{3}-C. The intra-assay coefficient of variation for the lipids and lipoproteins were: total cholesterol, 1.4%; HDL-C, 4.2%; HDL\textsubscript{3}-C, 5.0%; and triglycerides, 2.6%.

Ambulatory blood pressures were recorded in the nondominant arm with a Colin ABPM-630 automatic ambulatory noninvasive blood pressure monitor (Colin Medical Instruments Corp) and a standard-size adult blood pressure cuff. The Colin ambulatory monitor is virtually silent when the cuff inflates and has the capability of suppressing the display mode so participants are not able to observe their blood pressure reading when the machine cycles. Blood pressures were obtained by the oscillometric method and stored on a memory cassette until retrieval.

\textbf{Procedure}

Laboratory testing was conducted in a temperature-controlled, noise-attenuated room and began between 8 and 9 AM after an overnight fast. Participants had also abstained from alcohol and caffeine consumption for 18 hours and had not exercised since midnight. After securing informed consent, a registered nurse obtained height and weight. Maximal handgrip strength was assessed for each hand twice, and the average of the two was used. ECG electrodes and a blood pressure cuff were attached to the subject, and the subject was seated in a comfortable chair. A trained experimenter took several blood pressures with a mercury manometer and the IBS simultaneously. A registered nurse then inserted the indwelling catheter into the antecubital vein, using the dominant arm whenever possible. After insertion of the intravenous line, participants rested for 20 minutes, after which a 7-minute baseline data collection period occurred.

Three challenging tasks, two mental and one physical, were presented in fixed order with 15-minute rest periods between each task. During the initial baseline and intertask periods, the subjects listened to relaxing environmental sounds of the ocean through earphones. The first mental task was a mirror image tracing task that was both challenging and frustrating. Participants were asked to trace the outline of a star-shaped figure while looking only at its reversed image in a mirror. They were told to trace the figure as quickly and accurately as possible for 5 minutes.

The second mental task was the delivery of a videotaped speech. Subjects were told to pretend that they had been accused of shoplifting by a plainclothes policeman and to prepare a speech that they would give to a magistrate, defending their actions and indicating what the consequences should be for the plainclothes policeman. They were given 2 minutes to prepare the speech and 3 minutes to deliver the speech. They were told that their performance would be evaluated.

The physical stress task was a 2.5-minute isometric handgrip task using a Lafayette Instrument hand dynamometer. During this task, subjects were told to maintain 30% of their maximal handgrip measured at the beginning of the laboratory session using the nondominant hand. Performance was monitored by an experimenter, and subjects were advised when they were not maintaining the proper handgrip pressure on the device.

During tasks and rest periods, heart rate was monitored continuously. Blood pressure was assessed every 2 minutes during rest and every 1 minute during tasks. Blood samples were drawn continuously during the last 2 minutes of each rest and task period.

After the completion of the laboratory session, subjects were fitted with the ambulatory blood pressure monitor and instructed in the use of the monitor and the pocket diary. They then wore the monitor while at work for the remainder of the laboratory testing day and at work on the following day. The monitor was programmed to take blood pressures every 30 minutes for both days, and subjects were asked to make an entry in the diary each time a reading was taken.

\textbf{Statistical Analysis}

Laboratory heart rate and blood pressure values were averaged for each rest and task period. Pretask resting levels were used as the baseline values because they were lower than posttask levels. Change scores were calculated by subtracting baseline levels from task levels. Blood pressure measurements taken in the ambulatory setting between 8 AM and 8 PM were averaged into 2-hour blocks of time for both days.

ANOVA was used to evaluate group differences in sociodemographic and baseline characteristics. A series of (3 group)\(\times\)4 (period: baseline, mirror image tracing, speech, and isometric exercise) repeated-measures ANOVAs tested whether the tasks elicited significant changes from baseline. A series of (3 group)\(\times\)3 (stressor) repeated-measures ANCOVAs were conducted on change scores to compare the physiological responses of the three groups, controlling for baseline levels of the appropriate physiological parameter and BMI. Among women, age was significantly correlated with systolic and diastolic blood pressure changes only during the mirror image tracing task \((r=.45\) and \(r=.51\), respectively); therefore, analyses including this task were repeated with age as an additional covariate.

Some postmenopausal women had higher estradiol and lower FSH and LH levels than premenopausal women had (see below). Therefore, for those tasks that yielded significant differences between menopausal groups, we conducted partial correlations between task-induced changes and hormone levels to ascertain whether the group differences were paralleled by significant linear associations between stress responses and hormone levels.

As expected from previous data collected in our laboratory, the public speaking task elicited the greatest change in rate-pressure product and catecholamines (see Table 3), suggesting substantial activation of the sympathetic nervous system. Partial correlations were performed between the speech-induced changes in blood pressure, heart rate, and norepinephrine and levels of lipids and lipoproteins and years of formal education, partialling out appropriate baseline levels and BMI. Preliminary analyses of the ambulatory blood pressure levels did not show any effect of day of testing. Therefore, the ambulatory blood pressure levels averaged within 2-hour blocks were ana-
TABLE 1. Demographic and Anthropometric Characteristics of Men and Premenopausal and Postmenopausal Women

<table>
<thead>
<tr>
<th></th>
<th>Men (n=15)</th>
<th>Premenopausal Women (n=17)</th>
<th>Postmenopausal Women (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>44.1±0.40*</td>
<td>44.3±0.52*</td>
<td>49.7±0.82†</td>
</tr>
<tr>
<td>Height, in.</td>
<td>70.1±0.71*</td>
<td>64.0±0.89†</td>
<td>65.1±0.58†</td>
</tr>
<tr>
<td>Weight, lb</td>
<td>181.0±7.1*</td>
<td>139.7±4.6†</td>
<td>157.4±7.4‡</td>
</tr>
<tr>
<td>Body mass index, wt/ht²</td>
<td>25.9±0.78*</td>
<td>24.2±1.0*</td>
<td>26.0±1.0*</td>
</tr>
<tr>
<td>Education, y</td>
<td>19.3±0.85*</td>
<td>15.4±0.74†</td>
<td>17.0±0.91†‡</td>
</tr>
<tr>
<td>Hollingshead Job Classification</td>
<td>7.7±1.7*</td>
<td>7.1±2.2*</td>
<td>7.3±2.3*</td>
</tr>
</tbody>
</table>

*†Different superscripts indicate significant (P<.05) differences; the same superscript indicates no significant difference between values. Values are mean±SEM.

Analyzed by 3 (group)×8 (block) repeated-measures ANOVA. Because the groups differed in resting blood pressure during the laboratory protocol, analyses were repeated with laboratory resting blood pressure levels, BMI, and age as covariates. Post hoc Tukey's honestly significant difference multiple comparison tests and internal comparisons were used to identify significant differences between specific groups. Greenhouse-Geisser corrections were used in the repeated-measures designs. Unadjusted means and SEM are presented, with values of P<.05 considered to be statistically significant.

Results

Sample Characteristics

Table 1 shows the demographic and anthropometric characteristics of the sample. Postmenopausal women were somewhat older than the premenopausal women and men. Men were taller and weighed more than the women. Postmenopausal women were heavier than premenopausal women. There were no significant differences among groups in BMI. Although men had more years of formal education than the premenopausal women, they did not differ statistically from either group of women in their occupational status. The mean levels (and ranges) for the premenopausal and postmenopausal groups were 16.3 mIU/mL (range, 5.8 to 53.4) and 87.3 mIU/mL (range, 38.5 to 137.8) for FSH, 8.3 mIU/mL (range, 0.14 to 21.3) and 80.1 mIU/mL (range, 21.7 to 164.2) for LH, and 69.9 pg/mL (range, 22.0 to 175.0) and 18.5 pg/mL (range, 0.00 to 118.6) for estradiol, respectively.

Table 2 shows the mean baseline levels of cardiovascular, neuroendocrine, and metabolic parameters of the three groups as measured during the laboratory protocol. Men had higher systolic blood pressure than did premenopausal women, whereas postmenopausal women did not differ from men or premenopausal women. Men and postmenopausal women had higher levels of total cholesterol and LDL-C than premenopausal women had, and both groups of women had higher levels of HDL-C and HDL2-C than men had.

Influence of Stressors on Physiological Responses

Table 3 shows baseline and task levels of blood pressure, heart rate, and catecholamines averaged across the three groups. Relative to baseline values, task levels of blood pressure and heart rate increased during all tasks. The speech elicited significant increases in epinephrine and norepinephrine levels, whereas the mirror image tracing task elicited significant increases in epinephrine levels only.

TABLE 2. Laboratory Baseline Levels of Blood Pressure, Heart Rate, Catecholamines, Lipids, and Lipoproteins by Group

<table>
<thead>
<tr>
<th></th>
<th>Men (n=15)</th>
<th>Premenopausal Women (n=17)</th>
<th>Postmenopausal Women (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>112.7±2.6*</td>
<td>102.5±1.8†</td>
<td>109.7±2.3†‡</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>72.2±1.8*</td>
<td>67.3±1.7*</td>
<td>71.1±1.8*</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>64.7±2.7*</td>
<td>68.6±1.6*</td>
<td>69.1±2.2*</td>
</tr>
<tr>
<td>Epinephrine, pg/mL</td>
<td>67.5±9.1*</td>
<td>53.9±7.4*</td>
<td>45.1±7.8*</td>
</tr>
<tr>
<td>Norepinephrine, pg/mL</td>
<td>286.8±19.3*</td>
<td>285.5±26.9*</td>
<td>354.2±25.6*</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>195.5±8.5*</td>
<td>161.7±6.3†</td>
<td>200.1±7.6*</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>84.9±9.4*</td>
<td>62.5±8.3*</td>
<td>78.4±9.9*</td>
</tr>
<tr>
<td>LDL-C</td>
<td>130.6±8.6*</td>
<td>92.0±5.8†</td>
<td>122.5±6.8*</td>
</tr>
<tr>
<td>HDL-C</td>
<td>48.0±3.0*</td>
<td>57.2±2.7†</td>
<td>61.9±3.8†</td>
</tr>
<tr>
<td>HDL2-C</td>
<td>9.1±1.5*</td>
<td>16.3±2.0†</td>
<td>18.6±2.5†</td>
</tr>
</tbody>
</table>

bpm indicates beats per minute; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol. Values are mean±SEM.

*†Different superscripts indicate significant (P<.05) differences by Tukey’s honestly significant difference test; the same superscript indicates no significant difference between values.
Table 3 also reveals that the speech task elicited a larger systolic blood pressure, diastolic blood pressure, and heart rate response than did the mirror image tracing and a larger systolic blood pressure, heart rate, and epinephrine response than did isometric exercise. Isometric exercise elicited a blood pressure response that was greater than that of mirror image tracing.

**Group Influences on Stress-Induced Cardiovascular and Neuroendocrine Changes**

Table 4 shows the mean changes in cardiovascular and neuroendocrine measures during mental stress relevant to the hypotheses that postmenopausal women would show larger stress-induced changes than would premenopausal women and that postmenopausal women and men might exhibit no difference or small differences in stress-induced changes. Significant Group by Task interactions for systolic blood pressure, F(4,90)=3.5, P<.02, and diastolic blood pressure, F(4,90)=4.5, P<.004, showed that there were group differences in blood pressure change during mirror image tracing and speech tasks but not during isometric exercise. When age was included as a covariate, identical results were obtained. Postmenopausal women exhibited larger systolic and diastolic blood pressure responses to the mirror image tracing task and a larger diastolic blood pressure response to the speech task than did premenopausal women (Figs 1 and 2). Postmenopausal women also had larger systolic and diastolic blood pressure responses to the speech task and a larger systolic blood pressure response to the mirror image tracing task than did men (Figs 1 and 2).

Postmenopausal women and men had greater norepinephrine responses than the premenopausal women to...
all tasks (see Table 4), but group differences controlling for baseline levels of norepinephrine and BMI did not achieve statistical significance, F(2,32)=2.6, P=.08. Task-induced changes in epinephrine and heart rate did not vary across groups.

Correlations Between Mental Stress–Induced Responses and Reproductive Hormone Levels in Women

Among all women, estradiol levels were associated with changes in systolic and diastolic blood pressure during mirror image tracing (Table 5) and in norepinephrine during speech. FSH levels were associated with changes in systolic and diastolic blood pressures and norepinephrine during mirror image tracing and diastolic blood pressure and norepinephrine during speech. LH levels were associated with changes in diastolic blood pressure during mirror image tracing and diastolic blood pressure and norepinephrine during the speech. The correlations between age and hormone levels were high: r=.68 for FSH, r=.63 for LH, and r=−.38 for estradiol. When age was included as a covariate, the associations between blood pressure change and hormone levels became nonsignificant, although the correlation between norepinephrine change during speech and hormone levels was unchanged.

Group Influences on Ambulatory Blood Pressure Levels During the Workday

The group main effect for ambulatory systolic blood pressure, F(2,44)=3.5, P=.03, followed by internal contrasts, showed that men had significantly higher ambulatory systolic blood pressure levels across 2 consecutive workdays compared with the premenopausal women; men and postmenopausal women did not differ (Table 6). The group main effect for ambulatory diastolic blood pressure, F(2,44)=5.1, P=.01, revealed that both men and postmenopausal women had higher mean ambulatory diastolic blood pressure levels than did premenopausal women (Table 6). When statistical controls were introduced for the group differences in resting blood pressures at the laboratory session (taken after a rest period of 30 minutes), age, and BMI, similar results were obtained in the case of diastolic blood pressure, F=3.3, P=.04. Group differences in systolic blood pressure became nonsignificant (P=.53).

Associations Between Speech-Induced Responses and Risk Factors

In the full sample, partial correlations, controlling for appropriate baseline levels and BMI, showed that the greater the change in systolic (r=.28) and diastolic (r=.28) blood pressures during the speech, the higher
TABLE 5. Correlations Between Stress-Induced Change in Systolic and Diastolic Blood Pressure, Norepinephrine, and Reproductive Hormones

<table>
<thead>
<tr>
<th></th>
<th>FSH</th>
<th>LH</th>
<th>Estradiol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mirror Image tracing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>0.47*</td>
<td>0.29</td>
<td>-0.39*</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>0.53*</td>
<td>0.50*</td>
<td>-0.34*</td>
</tr>
<tr>
<td>Norepinephrine, pg/mL</td>
<td>0.41*</td>
<td>0.27</td>
<td>-0.19</td>
</tr>
<tr>
<td>Speech task</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>0.18</td>
<td>0.01</td>
<td>-0.26</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>0.39*</td>
<td>0.34*</td>
<td>-0.25</td>
</tr>
<tr>
<td>Norepinephrine, pg/mL</td>
<td>0.57*</td>
<td>0.54*</td>
<td>-0.42*</td>
</tr>
</tbody>
</table>

FSH indicates follicle-stimulating hormone; and LH, luteinizing hormone. *P<.05.

Discussion

The study evaluated indirectly the effects of reproductive hormone status on cardiovascular and neuroendocrine responses to mental and physical stressors presented in the laboratory and on ambulatory blood pressure levels throughout the workday. On the basis of previous findings, we expected that postmenopausal women would exhibit greater blood pressure and catecholamine responses to mental stress than would premenopausal women. We anticipated that this pattern of results would extend to measures of ambulatory blood pressure levels taken during the workday. Our expectations were partially confirmed. Postmenopausal women had greater blood pressure responses and tended to have greater norepinephrine responses to the two mental stressors than did premenopausal women. Subanalyses by partial correlation demonstrated that the greater the changes in norepinephrine responses to public speaking, the lower the levels of estradiol; and the greater the changes in blood pressure responses to the two mental stressors, the greater the FSH and LH levels and the lower the estradiol level (for mirror image tracing only). Importantly, premenopausal and postmenopausal women did not differ in their responses to the physical stressor, suggesting that mental stress was a unique elicitor of differences between the groups. Relative to premenopausal women, postmenopausal women had higher ambulatory diastolic blood pressure levels throughout the workday, even when statistical controls were introduced for BMI, resting blood pressure during the laboratory protocol, and age. These findings suggest that the postmenopausal women were more reactive to the stress of their work experience than were the premenopausal women. Taken together, these results replicate our previous study documenting the differences between premenopausal and postmenopausal women's cardiovascular responses to mental stress,11 and they demonstrate the differences between premenopausal and postmenopausal women's ambulatory blood pressure levels in the work environment.

Not anticipated were our findings comparing men and women. We had previously reported sex differences between young adult and middle-aged men and women (without regard to menopausal or job status) in their cardiovascular responses to mental stress.10,24 Unexpectedly, men in the present sample had smaller blood pressure responses to mental stress than did the postmenopausal women. However, men and postmenopausal women did exhibit similar norepinephrine responses to mental stress and equivalent ambulatory blood pressure levels. It is possible that the men's relatively low response to mental stress is because we deliberately selected working men and women and equated them for prestige of job classification, which has not been done in previous studies comparing men and women. It is also possible that elevated responses of postmenopausal women compared with men are a temporary response to changing hormone levels. Nonetheless, our findings are reminiscent of an unpublished report comparing cardiovascular reactivity of male and female cardiac patients: male patients exhibited smaller increases in heart rate and diastolic blood pressure to mental stress than did female patients. The authors of that report suggested that this pattern may contribute to women's worse prognosis after myocardial infarction.25

There are several possible mechanisms that may account for the influence of women's menopausal status.

TABLE 6. Mean Ambulatory Blood Pressure Levels According to Group

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Men</td>
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<td>Postmenopausal Women</td>
</tr>
<tr>
<td></td>
<td>(n=15)</td>
<td>(n=17)</td>
<td>(n=16)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>125.9±3.3*</td>
<td>117.4±2.1†</td>
<td>124.1±3.1††</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>76.4±1.8*</td>
<td>69.6±2.2††</td>
<td>75.5±3.2*</td>
</tr>
</tbody>
</table>

*†Different superscripts indicate significant (P<.05) differences in mean blood pressure by Tukey's honestly significant difference test; the same superscript indicates no significant difference between values. Values are mean±SEM.
on cardiovascular stress responses. One possible mechanism is that estrogens may mediate receptor sensitivity and/or number. Some animal studies have demonstrated diminished β-adrenergic receptor responsiveness to catecholamines under the influence of estrogens, and one human study has demonstrated that women have diminished peripheral vascular receptor sensitivity and/or density relative to men. Estrogens reduce the rate of catecholamine excretion by competitively inhibiting catechol-O-methyltransferase, one of the metabolic enzymes responsible for the degradation of catecholamines. Both of these actions prolong the biological activity of catecholamines and were illustrated in a study of sex differences in response to a metabolic stress. In that study, women had both reduced and prolonged recovery of a catecholamine response relative to men.

Estrogen may also be protective by direct effect on vessel wall biology. It is thought that estrogen may increase the release of endothelium-derived relaxing factor and prostacyclin from endothelial cells, thereby allowing for local vasodilatation and subsequently lower blood pressure and peripheral resistance. Consistent with this possibility are the results from primate studies showing that estrogen modulates impaired endothelium-mediated dilatation of atherosclerotic coronary arteries.

The significant association between cardiovascular reactivity to mental stress and levels of serum cholesterol, which is independent of BMI, confirms previous observations of an association in middle-aged men at risk for CHD because of behavioral risk factors or preexisting cardiovascular morbidity. We had previously reported no association between cardiovascular reactivity to mental stress and levels of serum cholesterol in a sample of young adult, healthy volunteers. Perhaps this lack of association is because of the age-associated alterations in lipid metabolism, and our previous volunteers were too young to show an association. Nonetheless, recall that the theoretical basis for our exploring this association was that the capacity to respond to stress with sympathetic nervous system activation would lead to elevated cardiovascular responses and to alterations in risk factors, including lipid metabolism. This hypothesis merits close scrutiny in future research.

The more years of formal education, the smaller the blood pressure responses to mental stress. This inverse relation is particularly interesting, considering that educational attainment protects against early cardiovascular disease and that individuals from lower socioeconomic status backgrounds may be exposed to considerable stress and be vulnerable to that stress. Our blood pressure results suggest that well-educated people, other factors being equal, respond with less blood pressure increase during stressful situations compared with less-educated people. The positive correlation between education and norepinephrine response to mental stress is in conflict with the blood pressure data; replication of these findings in future studies would be an impetus to explore possible mechanisms.

In summary, this study found that among healthy volunteers, postmenopausal women exhibit heightened blood pressure responses to mental stress relative to premenopausal women. Postmenopausal women and men exhibited similar and elevated ambulatory diastolic blood pressure responses relative to premenopausal women. The heightened cardiovascular stress responses of postmenopausal women may play a critical role in determining their risk of subsequent cardiovascular morbidity and mortality. Furthermore, if superimposed on an already diseased vasculature, large stress responses may explain the transition from subclinical to clinical disease in postmenopausal women. Clinical studies using hormonal manipulations in women would provide a strong test of the hypothesis that estrogens are cardioprotective via their modulation of stress responses. Awareness of the bias of some individuals, particularly postmenopausal women, to respond with heightened cardiovascular responses to stressful situations could help to identify a subset of persons who are at increased risk for clinical events. Behavioral interventions may have the potential to reduce that risk.

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