Early Cardiac Changes After Menopause

Giuseppe Schillaci, Paolo Verdecchia, Claudia Borgioni, Antonella Ciucci, Carlo Porcellati

Abstract—The mechanisms underlying the increased cardiovascular risk after menopause are incompletely known. To investigate whether menopause may induce left ventricular structural and functional adaptations in normotensive and hypertensive women, we compared in a case-control setting (1) 76 untreated hypertensive premenopausal women with 76 postmenopausal women and (2) 30 normotensive premenopausal women with 30 postmenopausal women. Subjects were individually matched by age (±5 years; range, 45 to 55), clinic systolic blood pressure (±5 mm Hg), and body mass index (±2 kg/m²). All subjects underwent 24-hour blood pressure monitoring and M-mode echocardiography. Age, clinic and daytime blood pressure, body mass index, and smoking habits did not differ between the paired groups. After menopause, blood pressure fall from day to night was lower in both normotensives (10/15% versus 16/21%) and hypertensives (12/17% versus 16/21%) (all P<0.01). Menopause was also associated with a greater left ventricular relative wall thickness (38.8% versus 35.1% in normotensives, 40.2% versus 37.5% in hypertensives) and a reduced midwall fractional shortening (17.3% versus 18.6% in normotensives, 16.6% versus 17.9% in hypertensives) (all P<0.05). We conclude that menopause is associated with blunted day-night blood pressure reduction, impaired left ventricular systolic performance, and concentric left ventricular geometric pattern. These findings are independent of presence or absence of high blood pressure. (Hypertension. 1998;32:764-769.)

Key Words: blood pressure monitoring, ambulatory ■ circadian rhythm ■ echocardiography ■ hypertension, arterial ■ hypertrophy ■ menopause

Premenopausal women have a lower risk of coronary heart disease than age-matched men, whereas after menopause the male-female ratio of coronary heart disease death declines.12 Data from the Framingham Study indicate a >2-fold age-adjusted increase in risk for coronary heart disease in postmenopausal compared with premenopausal women.3 Furthermore, young women with bilateral oophorectomy have an increased risk of coronary heart disease unless they are treated with estrogens.2 These observations, together with the favorable effect of hormonal replacement therapy on cardiovascular morbidity and mortality in postmenopausal women,4,6 have led to the assumption that ovarian hormones, especially estrogens, may protect women from coronary heart disease in the midlife and that their relative absence after menopause may contribute to accelerated progression of coronary artery disease.

The mechanisms of the beneficial cardiac and vascular effects of estrogens are multiple and incompletely known. Estrogens favorably affect lipid profile,4,7,8 and this mechanism could account for ≈25% to 50% of their beneficial effects on coronary heart disease.4 Estrogens preserve LDLs from oxidation9,10 and increase cellular resistance to the cytotoxic effects of oxidized LDL.10 Moreover, vascular reactivity improves after estrogen treatment in postmenopausal women.11,12 The possibility of a physiological effect of estrogens on myocardial cells has been raised after the recent characterization of transcriptionally active estrogen receptors in cardiac myocytes and fibroblasts.13 There is also evidence that sex hormones have important cardioregulatory effects, with sex-specific adaptations to cardiac stress.14

The structural and functional effects of menopause on the left ventricle, as well as the role of menopause in cardiac adaptation to hypertension, have not been specifically investigated. The present study was designed to assess left ventricular (LV) structural and functional adaptation to high blood pressure (BP) in a population of premenopausal and postmenopausal women with untreated essential hypertension, matched by age, BP, and body mass index in a case-control design. Two matched groups of normotensive women, before and after menopause, were also studied to assess the physiological changes induced by menopause in normotensive subjects.

Methods

The present study is an analysis of 152 women with essential hypertension, 76 premenopausal and 76 postmenopausal, drawn from a larger group of 2404 untreated hypertensive subjects (mean age, 53±12 years).15-17 A second case-control analysis was performed in 60 healthy normotensive subjects, 30 premenopausal and 30 postmenopausal. All subjects are included in the Progetto Iper tensione Umbria Monitoraggio Ambulatoriale (PIUMA) study, a prospective observational registry of morbidity and mortality in subjects with essential hypertension whose initial diagnostic workup includes 24-hour noninvasive ambulatory BP monitoring according
to a standardized protocol. Hypertensive subjects were referred to 3 participating centers for baseline evaluation by a group of general practitioners operating in Umbria in central Italy. Eligible subjects had clinic systolic BP \( \geq 140 \) mm Hg and/or diastolic BP \( \geq 90 \) mm Hg on \( \geq 3 \) visits at 1-week intervals and fulfilled all the following inclusion criteria: (1) no previous treatment for hypertension or withdrawal from antihypertensive drugs; (2) no clinical or laboratory evidence of heart failure, coronary heart disease, previous stroke, valvular defects, secondary causes of hypertension, or important concomitant disease; (3) good quality echocardiographic tracings; and (4) \( \geq 1 \) valid BP measurement per hour over the 24 hours. Normotensive subjects were members of the hospital staff or subjects examined for clinical checkup and found healthy. All had clinic systolic BP \(<140 \) mm Hg and diastolic BP \(<90 \) mm Hg on \( \geq 3 \) occasions and fulfilled the above points 2 to 4. All subjects gave informed consent for the study.

**Identification of Case and Control Subjects**

From the PIUMA database we identified all hypertensive women aged 45 to 55 years with normal menstrual cycles \((n=76)\). After all data concerning ambulatory BP and echocardiographic data were erased from the working copy of the computer file, 76 women in menopause for \( \geq 1 \) year were individually matched with premenopausal women by age (within 5 years), clinic systolic BP (within 5 mm Hg), and body mass index (within 2 kg\( \times \)m\(^{-2} \)). Menopausal status was assessed by questionnaire. Women with uncertain menopausal status, as well as subjects in menopause for \(<1 \) year, were excluded from the study. Diabetes mellitus (fasting glucose \( >7.8 \) mmol/L or hypoglycemic therapy) and estrogen use were further exclusion criteria. The same matching procedure was followed for normotensive premenopausal women aged 45 to 55 years \((n=30)\), who were matched with the same number of normotensive postmenopausal women.

**BP Measurement**

Clinic BP was measured by a physician in the hospital clinic with a mercury sphygmomanometer, with the subject sitting for 10 minutes. The average of 3 measurements was considered for the analysis. Ambulatory BP was recorded with an oscilometric device (models 90202 and 90207, SpaceLabs), set to take a reading every 15 minutes throughout the 24 hours. Normal daily activities were allowed and encouraged, and patients were told to keep their behaviors consistent according to the American Society of Echocardiography recommendations. Only frames with optimal visualization of interfaces and simultaneously showing septum, LV internal diameter, and posterior wall were used for reading. Tracings were read by 2 observers who were unaware of patients’ clinical data, and the mean value from \( \geq 5 \) measurements per observer was computed. The intraobserver and intratracing variabilities in our laboratory have been reported elsewhere. LV mass was calculated according to Devereux et al and normalized by both body surface area and by height\(^2\) to correct for the effect of overweight. Relative wall thickness was calculated as \(2 \times \)posterior wall thickness/LV internal diameter). LV mechanics was calculated at both the chamber level (as endocardial fractional shortening) and the midwall level, according to a geometric model that takes into account the nonuniform systolic thickening of LV wall. Fractional shortening was considered in both absolute terms and after correction for afterload, as a percentage of the predicted value on the basis of the regression equation between end-systolic meridional wall stress and fractional shortening in a group of 121 normotensive women. The 2-dimensional study showed a symmetrical LV contraction in all the subjects, and thus LV volumes were calculated with the use of the Teichholz formula, which proved accurate in the absence of regional abnormalities of contraction. Cardiac output (stroke volume \( \times \)heart rate) was indexed by body surface area to obtain cardiac index. Total peripheral resistance was derived as follows: \(80 \times \)mean BP/cardiac index.

**Statistical Analysis**

Data were stored with a DBASE 5.0 for Windows package (Borland Inc), and statistical analyses were done with the SPSS/PC+ software, version 3.0 (SPSS Inc). The paired groups (normotensive premenopausal women versus normotensive postmenopausal women, hypertensive premenopausal women versus hypertensive postmenopausal women) were compared by Student’s \( t \) test and \( \chi^2 \) test when appropriate. \( P \) levels \(<0.05 \) were considered statistically significant. Data are presented as mean (SD).

**Results**

Some demographic and clinical characteristics of the study population are reported in Table 1. By matching, age and

**TABLE 1. Demographic and Clinical Characteristics of Subjects**

<table>
<thead>
<tr>
<th>Data</th>
<th>Premenopausal</th>
<th>Postmenopausal</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>49.4 (3)</td>
<td>49.8 (3)</td>
<td>0.64</td>
</tr>
<tr>
<td>Body mass index, kg - m(^{-2})</td>
<td>27.3 (4)</td>
<td>26.7 (4)</td>
<td>0.49</td>
</tr>
<tr>
<td>Body surface area, m(^2)</td>
<td>1.75 (0.1)</td>
<td>1.73 (0.1)</td>
<td>0.44</td>
</tr>
<tr>
<td>Alcohol intake, g/d</td>
<td>12 (19)</td>
<td>4 (8)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>27</td>
<td>40</td>
<td>0.28</td>
</tr>
<tr>
<td>Duration of hypertension, y</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Never treated, %</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.40 (1.0)</td>
<td>5.82 (1.2)</td>
<td>0.16</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.41 (0.3)</td>
<td>1.28 (0.3)</td>
<td>0.22</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.21 (0.7)</td>
<td>1.61 (0.8)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Data are expressed as mean (SD).
body mass index were virtually identical before and after menopause in the paired groups. The groups were also comparable in terms of smoking habits, body surface area, lipid profile, duration of hypertension, and prevalence of subjects never treated for hypertension. Normotensive premenopausal women had a slightly greater daily alcohol intake than their postmenopausal counterparts. Among postmenopausal women, the average time interval from menses cessation was 5.8 years (SD 5) in normotensive subjects and 5.1 years (SD 4) in hypertensive subjects. In the hypertensive postmenopausal group, hypertension had been observed for the first time, as reported by questionnaire, before menopause in 29 women and thereafter in the remaining 47 women.

Blood Pressure

By protocol, clinic BP was identical before and after menopause in the 2 groups (Table 2). Awake BP was also similar in the study groups. In hypertensive subjects, menopause was associated with a higher nocturnal systolic and diastolic BP (P<0.009 and P<0.008, respectively) and a significantly reduced percent day-night BP change (P<0.001 for systolic BP, P<0.004 for diastolic BP). As shown in Figure 1, during nocturnal sleep systolic and diastolic BP fell to a lesser extent in the menopause group than in premenopausal subjects.

These finding were similar to those observed in normotensive subjects, who showed a significant reduction in BP change from day to night after menopause (both P<0.003). Duration of sleep, as well as clinic and ambulatory heart rate, was not significantly different in the study groups.

LV Structure and Function

Hypertensive Subjects

As shown in Table 3, LV relative wall thickness was significantly greater after menopause than in ovulating women (P<0.04). This concentric geometric pattern resulted from a small increase in wall thickness bordering statistical significance (P=0.08 for interventricular septum, P=0.06 for posterior wall), without obvious changes in LV internal dimension. No significant increase in LV mass was observed in postmenopausal subjects (P=0.14 after adjustment for body surface area, P=0.13 after adjustment for height²). As shown in Figure 2, LV systolic performance was reduced after menopause when calculated at the midwall level both in absolute terms (16.6% versus 17.9%; P<0.004) and after correction for afterload (93% versus 100%; P<0.007). No significant difference was found when LV function was measured at the chamber level as endocardial fractional shortening (P=0.06 both before and after correction for afterload). Subjects in menopause had a marginally lower cardiac index (P=0.08) and a mildly increased total peripheral resistance, bordering statistical significance (P=0.07).

Normotensive Subjects

Menopause was associated with LV changes not dissimilar from those observed in hypertensive subjects (Table 3). Postmenopausal subjects had an increased relative wall thickness (P<0.03) without significant increase in LV mass (P<0.46). After menopause, midwall LV systolic performance was significantly reduced compared with premenopausal women (P<0.05 in absolute terms, P<0.03 after correction for afterload) (Figure 2), as well as afterload-corrected endocardial fractional shortening (P<0.05). Postmenopausal women had a lower cardiac index (P<0.03) and a higher total peripheral resistance (P<0.02) than premenopausal subjects.
Discussion

Postmenopausal women with essential hypertension had a more concentric LV geometric pattern and a decreased midwall systolic function than premenopausal women. Similar menopause-induced changes were noted in healthy normotensive women. We analyzed 2 large groups of hypertensive and normotensive subjects. In each group, premenopausal women were accurately matched with postmenopausal women by age, BP, and body mass index in a case-control design.

To our knowledge, LV structure and function have never been compared in age-matched women before and after menopause. Some indirect conclusions can be drawn from separate analyses of age-related LV changes in men and women. In a small study by Garavaglia et al.28 performed in hypertensive subjects, 15 premenopausal women had lower relative wall thickness and higher systolic function indexes than age-matched men. In contrast, no sex difference in LV structure and function was observed in 14 older postmenopausal women compared with 14 age-matched men. In particular, relative wall thickness in women was 38.5% and 40.8% before and after menopause, respectively (corresponding values in men were 40.5% and 40.8%).28 An increase in LV wall thickness has been reported in normotensive women after menopause, but the confounding effect of age and overweight could not be excluded.29,30 In the highly selected "healthy" subjects from Framingham (14% of the total population), LV mass decreased slightly with age in men and increased in women; this finding in women also held in a multivariate analysis.31 Women with essential hypertension have a greater cardiac output than age- and BP-matched men, and this difference disappears after age 45 years.32 Similarly, in normotensive women, Doppler aortic flow indexes of LV systolic function show a progressive and time-dependent decrease after menopause,33 which can be reversed after estrogen therapy.34 de Simone et al.35 reported that the difference in LV mass between men and women decreased after 55 years, but, at variance with the previous studies, LV internal diameter tended to increase in women with age. The relatively small sample size of that study (23 women and 28 men aged ≥55 years) does not allow complete exclusion of the effect of chance.

Taken together, these data are compatible with the hypothesis of an association in humans between menopause and concentric LV geometric pattern with reduced LV systolic function, but the confounding effect of age and overweight on these relations remained elusive. The present study allowed us to control the confounding effect of several variables, including clinic and awake BP, age, and obesity. Our data support the view that menopause is independently associated with early geometric and functional alterations of the left ventricle in hypertension, and the consistency of these data in normotensive as well as in hypertensive women strongly suggests an independent physiological effect of menopause.

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**TABLE 3. Echocardiographic Characteristics of Subjects**

<table>
<thead>
<tr>
<th>Data</th>
<th>Normotensive Subjects</th>
<th></th>
<th>Hypertensive Subjects</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Premenopausal (n=30)</td>
<td>Postmenopausal (n=30)</td>
<td>P</td>
<td>Premenopausal (n=76)</td>
</tr>
<tr>
<td>Interventricular septum, mm</td>
<td>9.3 (1)</td>
<td>9.7 (1)</td>
<td>0.24</td>
<td>10.3 (2)</td>
</tr>
<tr>
<td>Posterior wall, mm</td>
<td>8.3 (1)</td>
<td>8.9 (1)</td>
<td>0.08</td>
<td>9.0 (2)</td>
</tr>
<tr>
<td>LV internal dimension, mm</td>
<td>47.5 (4)</td>
<td>46.2 (4)</td>
<td>0.19</td>
<td>48.6 (5)</td>
</tr>
<tr>
<td>LV mass/BSA (g×m⁻²)</td>
<td>81.3 (17)</td>
<td>84.5 (16)</td>
<td>0.46</td>
<td>96.5 (23)</td>
</tr>
<tr>
<td>LV mass/height² (g×m⁻²)</td>
<td>39.4 (9)</td>
<td>40.5 (9)</td>
<td>0.66</td>
<td>46.0 (14)</td>
</tr>
<tr>
<td>Relative wall thickness, %</td>
<td>35.1 (5)</td>
<td>38.8 (8)</td>
<td>&lt;0.03</td>
<td>37.5 (7)</td>
</tr>
<tr>
<td>FS, %</td>
<td>39.1 (6)</td>
<td>37.6 (6)</td>
<td>0.37</td>
<td>39.5 (8)</td>
</tr>
<tr>
<td>Afterload-corrected FS, %</td>
<td>103 (9)</td>
<td>98 (11)</td>
<td>&lt;0.05</td>
<td>110 (12)</td>
</tr>
<tr>
<td>Midwall FS, %</td>
<td>18.6 (2)</td>
<td>17.3 (3)</td>
<td>&lt;0.05</td>
<td>17.9 (3)</td>
</tr>
<tr>
<td>Afterload-corrected midwall FS, %</td>
<td>101 (10)</td>
<td>94 (15)</td>
<td>&lt;0.03</td>
<td>100 (15)</td>
</tr>
<tr>
<td>Cardiac index, L×min⁻¹×m⁻²</td>
<td>3.11 (0.6)</td>
<td>2.74 (0.7)</td>
<td>&lt;0.03</td>
<td>3.42 (0.9)</td>
</tr>
<tr>
<td>TPR index, 10¹ dynes×s×m²×cm⁻⁵</td>
<td>2.61 (0.5)</td>
<td>3.07 (0.8)</td>
<td>&lt;0.02</td>
<td>2.94 (0.8)</td>
</tr>
</tbody>
</table>

BSA indicates body surface area; FS, fractional shortening; and TPR, total peripheral resistance. Data are expressed as mean (SD).

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**Figure 2.** LV fractional shortening assessed at the midwall level in age- and BP-matched premenopausal (●) and postmenopausal (○) women.
As a measure of myocardial function we used stress-corrected midwall fractional shortening, which is independent of afterload and ventricular geometry.

A few possible mechanisms can explain our findings. First, sex hormones have important direct effects on the myocardium. In a study by Scheuer et al. in isolated rat hearts, postpubertal gonadectomy induced a reduction in myocardial contractile function in female subjects, which was reversed after estrogen replacement but not after progesterone replacement. Gonadectomy in both sexes induces a reduction of Ca$^{2+}$-myosin ATPase, with a shift from V1 to V3 isofrom. Accordingly, intrinsic contractile performance of papillary muscles is depressed in male rats compared with female subjects. Recently, functionally active estrogen receptors have been identified in rat neonatal myocardial cells. Thus, estrogen could exert a positive inotropic effect, and chronic estrogen deprivation—the identifying mark of menopause—might be a basic mechanism of decreased LV systolic function after menopause (Figure 2).

Second, there is growing evidence that estrogens exert a favorable effect on arterial vasomotility in women. Estrogen reduces vascular smooth muscle cell hyperplasia and collagen biosynthesis in animal studies. Endothelium-dependent vasodilation is impaired after menopause and restored by estrogen treatment. Recently, estrogen has been shown to reduce the pulsatile vascular afterload by decreasing the carotid late augmentation of systolic BP, an index of arterial stiffness. After menopause, the cessation of the beneficial effects of estrogen on arterial vasodilation and structure might determine LV structural changes. Arterial hypertrophy may promote cardiac hypertrophy, at least in part by causing an earlier return of reflected pressure waves from the peripheral circulation. Arterial stiffening is associated with LV remodeling, but not hypertrophy, independently of BP, and our finding of increased LV relative wall thickness, but not mass, after menopause is in keeping with those data.

Third, we observed a blunted BP reduction from day to night in postmenopausal compared with premenopausal subjects. This implies a longer duration of exposure to high BP levels throughout the 24 hours, with potential implications on structural and functional cardiac adaptation to hypertension. An increased LV mass and relative wall thickness have been described in hypertensive subjects whose BP does not fall at night compared with those with a normal sleep BP reduction, and this phenomenon is particularly evident in women.

Fourth, after menopause blood viscosity increases, with consequent potential reduction in circulating volume and LV chamber size. However, we could not investigate this possibility in the present study.

In conclusion, menopause is associated with early structural and functional manifestations of hypertensive heart disease that are independent of age, obesity, clinic BP, ambulatory BP, and other confounding factors. Normotensive women show comparable menopause-associated LV changes. These findings support the role of estrogen deprivation as an important determinant of early cardiac changes in hypertensive and normotensive women. Large outcome studies are needed to clarify the prognostic relevance of these data.

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References


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