Menopause and Hypertension: An Age-Old Debate
Megan Coylewright, Jane F. Reckelhoff and Pamela Ouyang

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Menopause and Hypertension
An Age-Old Debate
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Premenopausal women (pre-MW) have lower blood pressure (BP) than age-matched men, and women have higher rates of hypertension than men as they age. These findings suggest that gender or sex hormones have a prominent role in hypertension. Determining the role of sex hormones in the pathogenesis or progression of hypertension is complex given the effects of aging on the cardiovascular system and its relationship to other powerful risk factors such as body weight and cholesterol level. Longitudinal and cross-sectional studies report conflicting results concerning the role of menopause in the pathogenesis of hypertension. Large randomized trials of hormone replacement therapy (HRT) have called into question the long assumed protective effect of estrogen in heart disease risk. There are excellent reviews on the effects of gender and sex hormones on vascular tone and pathophysiologic abnormalities associated with hypertension in animals. This review focuses on studies in postmenopausal women (PMW), the relationship between menopause and hypertension, factors contributing to hypertension in PMW, and discussion of identification and treatment of hypertension in PMW.

Relationship Between Gender, Menopause, and Hypertension

Studies Indicating Menopause Leads to Increasing Hypertension
Cross-sectional studies suggest a relationship between menopause and serum cholesterol (Table). Both systolic and diastolic BP are reported to be related to menopause independent of age, body mass index (BMI), pulse rate, and HRT, and PMW had greater odds of being hypertensive than pre-MW (OR 2.2, \( P = 0.03 \)). In addition, the association between BP and age is steeper in PMW. Longitudinal cohort studies also demonstrated a relationship between menopause and hypertension. In a study of 315 women and age- and BMI-matched men followed for 5 years, PMW had higher systolic BP at baseline and systolic BP increased by approximately 5 mm Hg over 5 years of follow-up only in the peri- and PMW. The rise exclusively involved systolic pressure suggesting underlying decreased arterial compliance.

The association between BP and use of HRT was assessed in PMW who had never used HRT and 77 who had received continued HRT. Age at first examination, time in the study, and HRT predicted change in BP during 5.7 years of follow-up. Systolic and diastolic BP decreased to a lesser extent among HRT-users compared with nonusers with the greatest difference in older women, indirectly supporting a role for ovarian senescence in the development of hypertension.

Studies Indicating No Relationship Between Menopause and Hypertension
Other studies suggest that the apparent relationship between menopause and hypertension is explained by other factors including age (Table). An epidemiological study including 568 pre- and PMW, evaluated at 2 time periods separated by 16 years, showed that the higher systolic BP and cardiovascular morbidity and mortality seen in PMW was accounted for by age. Whether menopause is surgically induced or natural may influence subsequent risk of coronary heart disease. Bilateral oophorectomy without subsequent HRT, but not natural menopause or oophorectomy with subsequent HRT, has been associated with an increased risk of coronary heart disease. One longitudinal study suggested that in healthy normotensive women ovarian senescence protects against increasing BP with a negative association between years after menopause and systolic and diastolic BP. Aging was associated with a non-significant increase in systolic BP only; however, increased BMI was associated with hypertension. The study participants were a select group: only 10% of the eligible cohort of more than 4000 responded to invitation to participate, and of those, 402 were excluded because of medications that impacted BP, metabolism...
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<tr>
<th>Author, Publication Year</th>
<th>Study Population</th>
<th>Menopause Status</th>
<th>Study Design</th>
<th>Association/Conclusion</th>
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<tr>
<td>Weiss 19727</td>
<td>897 women; age 40–51 years</td>
<td>Pre- and postmenopausal</td>
<td>Cross-sectional</td>
<td>Increasing DBP is related to menopause, independent of age; no effect of time since menopause</td>
<td>US HES cohort.</td>
<td>Questionnaire for menopause. Limited accounting of confounders e.g. BMI, race. Average of only 3 BP measurements.</td>
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<tr>
<td>Staessen 19898</td>
<td>462 women; age 35–59 years</td>
<td>Pre- and postmenopausal</td>
<td>Cross-sectional</td>
<td>After stratifying by age and BMI, odds of hypertension for postmenopausal women compared to premenopausal women was 2.2 (95% CI 1.1–4.4, P=0.03), Relation between SBP and age steeper in menopausal than premenopausal women</td>
<td>Stratified by 3 age groups and 2 strata of BMI. BP from average of 10 measurements.</td>
<td>Questionnaire for menopause.</td>
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<tr>
<td>Owens 199379</td>
<td>34 women and 15 men; age 40–55 years</td>
<td>Pre- and postmenopausal</td>
<td>Cross-sectional</td>
<td>Postmenopausal women had higher stress-induced SBP and DBP rises than premenopausal women or men. Diastolic BP was higher in post-menopausal women and men compared to pre-menopausal women</td>
<td>Ambulatory BP monitor and standardized mental and physical challenges</td>
<td>Small size of sample</td>
</tr>
<tr>
<td>Zanchetti 200515</td>
<td>18,326 women; age 46–59 years</td>
<td>Pre-, peri-, and postmenopausal</td>
<td>Cross-sectional</td>
<td>SBP and DBP higher in postmenopausal women, association evident only among women in the younger age groups (46–49 years); P&lt;0.0001</td>
<td>Large cohort. The 2-year span subgroups reduce age difference among pre-, peri- and post-menopausal groups.</td>
<td>Three BP measurements in 505 general practitioners' offices</td>
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<tr>
<td>Staessen 19977</td>
<td>315 women, matched to 315 men by age and BMI; age 30–70 years</td>
<td>166 pre-, 44 peri-, 105 postmenopausal</td>
<td>Prospective</td>
<td>SBP rose nearly 5 mm Hg per decade more (P&lt;or=0.05) in peri- and postmenopausal than in premenopausal women. These trends were not found in DBP in women, or in SBP or DBP in men.</td>
<td>Median follow-up of 5.2 years. Ambulatory 24-hour monitoring used in the follow-up measurement. FSH levels at follow-up</td>
<td></td>
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<tr>
<td>Scuteri 200110</td>
<td>226 women; mean age 64 ± 10 years</td>
<td>Pre-, peri-, and postmenopausal evaluating association with use of HRT</td>
<td>Prospective</td>
<td>Postmenopausal women on HRT have a smaller increase in SBP over time; most pronounced among older women</td>
<td>Well characterized cohort within Baltimore Longitudinal Study of Aging (BLSA)</td>
<td>Predominantly white, educated volunteers. Observational study so there may be unaccounted differences between HRT users and non-users</td>
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(Continued)
of calcium, or timing of menopause. Careful selection of healthy normotensive individuals may reduce confounding, but inclusion of these individuals may introduce other biases and reduce the generalizability of the findings.

Relative Contribution of Menopause or Aging to Hypertension in PMW

Conflicting findings may result from differences among cohorts, including sample size, age ranges, length of time postmenopause, use of datasets not designed to study menopause, and reliance on questionnaires. Surgically PMW were often included, without considering the hormonal differences in natural and surgical menopause. Finally, both cross-sectional and longitudinal analyses are subject to confounding; the former because of inability to assess temporal relationships and the latter because of environmental changes or changes in medical management over time.

Given these inconsistencies, a cross-sectional analysis was done in more than 18 000 Italian women, aged 46 to 59 years, that found a significant, but clinically small, increase in both systolic and diastolic BP of 3.4/3.1 mm Hg among PMW, which was independent of age, BMI, smoking, or HRT, and was only evident at younger menopausal age. The difference in BP may be underestimated given the higher prevalence of treated hypertension in PMW (35%) compared with pre-MW (20%). However, menopausal effects

Table. Continued

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<td>Casiglia 199611</td>
<td>568 Italian women: At follow-up: pre-menopausal mean age 40 ±4 years; post-menopausal mean age 61 ±8 years</td>
<td>Pre- and postmenopausal</td>
<td>Prospective</td>
<td>After controlling for age, there is no difference between pre- and postmenopausal women in relation to hypertension or cardiovascular risk</td>
<td>Time span of 16 years. Age-adjusted data presented. Age-matched cohort showed similar lack of association between menopause and hypertension. Only natural menopause considered, none on HRT.</td>
<td>Only last of 3 office BP measurements used.</td>
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<tr>
<td>Luoto 200012</td>
<td>3,800 women; age 45–64 years</td>
<td>Peri- and postmenopausal</td>
<td>Prospective</td>
<td>Looking specifically at the peri-menopausal period, SBP did not differ from postmenopausal women</td>
<td>ARIC cohort followed for 6 years. Both White and African-Americans included.</td>
<td>No data on role of menopause. Predominantly white, highly educated and health conscious group of volunteers</td>
</tr>
<tr>
<td>Pearson 199780</td>
<td>1307 men and 333 women. Men aged 17–97 years; women aged 18–93 years</td>
<td>Pre-, peri-, and postmenopausal</td>
<td>Prospective</td>
<td>There was not a greater increase in BP rise over time compared to men</td>
<td>BLSA cohort are well-characterized.</td>
<td>No data on role of menopause. Predominantly white, highly educated and health conscious group of volunteers</td>
</tr>
<tr>
<td>Colditz 198773</td>
<td>121,700 women; age 30–55 years</td>
<td>Pre- and postmenopausal</td>
<td>Prospective</td>
<td>Naturally postmenopausal women, after controlling for age and smoking, were not at greater risk for coronary heart disease; those with surgical menopause did have a higher risk (RR 2.2) but this was eliminated with HRT</td>
<td>16-year follow-up with biannual questionnaires for cardiovascular outcomes. Adjudicated medical records review.</td>
<td>Observational study. Cannot exclude unaccounted differences between women with and without oophorectomy</td>
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Menopause associated with lower BP

van Beresteyn 198914 | 193 women; age 49–54 years; all pre- or ≤2 years post-menopausal | Pre- and postmenopausal | Prospective | SBP and SBP were negatively associated with years from menopause (SBP: 1.34 mm Hg per year and DBP: 0.63 mm Hg per year) | Seven-year follow-up. | Highly selected small cohort of healthy normotensive women |

BMI indicates body mass index; CVD, cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure. HRT, hormone therapy; RR, risk ratio; FSH, Follicle stimulating hormone; US HES, United States Health Examination Survey of adults; ARIC, Atherosclerosis Risk In Communities.
appear to be small and may be masked by age-related changes that increase BP. Careful large longitudinal studies may add further information.

Factors Contributing to Hypertension in PMW

We review major data on mechanisms postulated to contribute to the development of hypertension after menopause (Figure 1) and discuss mechanisms by which sex hormone changes related to menopause may contribute to postmenopausal hypertension (Figure 2).

Endothelial Dysfunction

Endothelial dysfunction, with reduction in vasodilators modulating vascular tone, is associated with diseases including hypertension and atherosclerosis, and may be one mechanism by which estrogen deficiency may result in hypertension. In a prospective study of 952 PMW, followed for 3.6 years, each one-unit decrease in flow-mediated dilation (FMD), measured by high resolution ultrasound, increased the risk of developing hypertension by 16%.16 In a second study endothelium-dependent vasodilation to acetylcholine decreased with age in hypertensive subjects, with a slower decline in pre-MW, compared with men.17 The greatest rate of decline in FMD occurred in PMW when compared with men ($P<0.01$) and pre-MW ($P<0.001$). The endothelium-independent (nitroprusside) response did not differ by sex or menopausal status. In normotensive women, age-related impairment of endothelial function was only seen after menopause.

Men and PMW may have less endogenous nitric oxide (NO) production, shown by less vasoconstriction following inhibition of NO synthase by L-N-monomethyl-arginine (L-NMMA), than pre-MW. After estrogen therapy, L-NMMA resulted in greater constriction consistent with estrogen restoring vascular NO activity to levels seen in pre-MW.18 Other studies have shown improvement in endothelial function with estrogen therapy with a greater improvement in hypertensive PMW.19

Treatment of postmenopausal hypertension can improve FMD and is associated with a better cardiovascular outcome.20 Hypertensive PMW who experienced a significant increase in FMD (>10% baseline) after nearly 6 years of antihypertensive therapy experienced fewer cardiovascular events than those without FMD improvement (3.5 per 100 person-years versus 0.51, $P<0.0001$). Thus, impaired FMD may identify particularly high-risk hypertensive PMW.

Acute estrogen deprivation after oophorectomy in healthy women results in impaired endothelium-dependent vasodilation as a result of reduced NO availability.21 Estrogen therapy improves endothelium-dependent vasodilation after oopho-
rectomy and also natural menopause. However, among a broader sample of PMW, HRT results in improved FMD only among women with no cardiovascular risk factors.

**Arterial Stiffness**
Increased arterial stiffness coincides with menopause. In a random sample of more than 300 women and 300 men, PMW showed higher carotid-femoral pulse wave velocity (PWV) and larger common carotid artery diameters after adjustment for age, BMI, and smoking, indicating increased arterial stiffness which may explain the greater rise in systolic pressure among PMW. A study of 3149 women, ages 21 to 94 years, evaluated the relationship between age, menopause, and arterial stiffness assessed by brachial-ankle PWV. Women, aged 45 to 56 years, who were 6 years from menopause, were most likely to be in the highest tertile of PWV; this was independent of age and other cardiovascular risk factors. However, other investigators have not found sex differences in arterial wall properties with aging.

**Renin-Angiotensin System**
The renin-angiotensin (RAS) system is an important regulator of BP and fluid and electrolytes. Estradiol may provide cardiovascular protection by controlling components of the RAS, including decreasing AT1 receptor expression in vessels and kidney and reducing the activity of angiotensin I-converting enzyme (ACE).

The role of the RAS in hypertension in PMW is less clear than in animal studies. A placebo-controlled study of 2 years of estrogen therapy found no correlation between BP and plasma renin activity (PRA). PRA increased during oral, but not transdermal, estradiol administration. Other small studies have shown similar results, though some show decreased ACE activity with oral HRT.

The regulation of the prorenin and renin may be affected by gonadal hormones. Ovarian production of prorenin in response to gonadotropins has been reported. The effect of estrogen on prorenin and renin appear complex. Studies in hypertensive individuals may be complicated by antihypertensive drugs that inhibit the RAS.

**Oxidative Stress**
An increase in oxidative stress can result from increased production of reactive oxygen species (ROS) or decreased ability to neutralize these reactive molecules. Gender differences in oxidative stress have been found with higher levels in males. Gonadectomy decreased urinary H2O2 excretion in male SHR and increased H2O2 excretion in females, suggesting that testosterone increases whereas estrogen suppresses total body oxidative stress. In vitro and animal models have shown that estrogen modulates prooxidant and antioxidant enzyme expression and activity, including NAD(P)H oxidase and superoxide dismutase, inhibiting production of ROS. It is postulated that the postmenopausal estrogen-deficient state is associated with increased ROS contributing to vasoconstriction and hypertension.

Whether increased ROS is present with menopause has not been unequivocally demonstrated. Increased nitrotyrosine, a marker of endogenous peroxynitrite, and decreased nitrosothiols, consistent with less NO bioavailability, were reported in PMW compared with pre-MW. However, the contribution of menopause could not be distinguished from that of age. Another oxidative stress marker is F2-isoprostane, produced by free radical–induced peroxidation of arachidonic acid and has been considered a marker of in vivo ROS.

Recently, investigators reported F2-isoprostanes were not elevated in PMW compared with pre-MW, and, contrary to expectations, were positively associated with levels of metabolites of estradiol.

Estrogens, including estradiol and estrogen metabolites, decrease ROS by scavenging free radicals. Whether HRT in PMW protects against oxidative stress-associated diseases is unknown.

**Salt Sensitivity**
Salt sensitivity increases with age in both sexes and is likely mediated by impaired vasodilation of the renal circulation, possibly because of reduced NO availability, increased vasoconstriction response to angiotensin II, or attenuation of the conversion of L-arginine to NO in the renal vasculature endothelium.

PMW appear to be more salt sensitive than pre-MW, and surgical menopause is associated with development of salt sensitivity. Salt sensitivity of systolic BP in healthy PMW not receiving HRT may be related to reduced bioavailability of NO associated with increased levels of the NO synthase antagonist, asymmetrical dimethyl-L-arginine. Treatment with transdermal estradiol in PMW was associated with a decrease in salt sensitivity of BP.

Low sodium diets decrease BP in experimental and real-world settings. Thus lifestyle behaviors including low sodium diet and exercise are recommended for individuals with hypertension.

**Obesity**
A large cross-sectional study showed an independent association between BMI and hypertension in women, aged 46 to 59 years. In a Finnish prospective population-based study of 9485 perimenopausal women not on antihypertensive therapy, predictors of hypertension over 5-year follow-up included baseline weight, weight increase, and PM status at baseline. Overweight has a stronger association with hypertension in pre-MW, whereas age has a stronger association in PM non–hormone users.

The mechanisms by which obesity is associated with hypertension include increased sympathetic overactivity that appears closely associated with abdominal visceral fat. Greater sympathetic activity increases renin release and angiotensin II formation, which in turn increases adrenal aldosterone production with resultant sodium retention. Increased visceral fat is associated with increased inflammatory mediators, increased oxidative stress, and decreased endothelial vasodilatation.

It is not clear whether menopause itself results in an increase in BMI. Although perimenopausal women and those with surgical menopause have been found to have higher BMI than pre-MW when controlling for age, physical activity and race/ethnicity were much stronger predictors of BMI.
Genetic Factors Influencing Hypertension

Genetic factors account for 30% to 50% of interindividual variability in BP. Hypertension is most likely a polygenetic disorder with each of the genes contributing modestly to BP. It is possible that menopause might provide the environmental trigger for the expression of certain genetic susceptibilities. Polymorphisms affecting a number of pathways involved in hypertension have been studied. While this is not an exhaustive review of the literature on genetics and hypertension, a few pertinent studies are reviewed.

Sex-specific determinants of genetic susceptibility that are distinct from sex hormone–mediated attenuation of sex-common determinants have been found. Several investigators have reported sex specific associations between human hypertension and polymorphisms of components of the RAS, aldosterone synthase, and NO synthase, although not in all populations studied. A study evaluating the relationship between the extremes of BP with 35 loci that have physiological roles in the regulation of BP described several gene-by-gender interactions. In women, polymorphism at the β1-adrenergic receptor and α2A adrenergic receptor contributed to BP, and in men polymorphism of β2-adrenergic receptor and angiotensinogen were associated. Polymorphism of genes regulating sodium reabsorption, such as adducin-1, have been associated with BP and hypertension. Gene-environment interactions have been shown including BMI and salt intake.

Other studies have also focused on pathways that might be implicated in sex hormone–related associations with hypertension. Gender-specific contributions of estrogen-related genes to BP variation have been described. Inactivating mutations in the follicle-stimulating hormone (FSH) receptor (FSHR) gene may cause hereditary hypergonadotropic ovarian failure. Polymorphisms in the human FSHR gene have been linked to essential hypertension in women. Other candidates in the testosterone-estradiol pathway have been investigated. In a case-control study of hypertension, associations between aromatase CYP19A1 gene variants and hypertension were found only in women, and this association was dependent on BMI. No association with menopause was found, suggesting that the effect of CYP19A1 variants on BP may be mainly related to aromatase activity in adipose tissue.

Gene-gender and gene-environment interactions impact hypertension in women. Menopause may provide an important environmental trigger resulting in genetic influences that mediate hypertension in women. These findings also raise the potential that antihypertensives may have different efficacy based on the gender and genetic background.

Current Clinical Issues

Most women will develop hypertension in their lifetime, and women who develop hypertension at a younger age are at higher risk of adverse cardiovascular events. The prevalence of hypertension rises more steeply in women than men after middle age. A study of women aged 45 years or older and initially free of cardiovascular disease showed that one third of women who were normotensive at baseline developed hypertension during the 10 year follow-up. Half the women with high-normal BP (130/85 to 138/89 mm Hg) developed hypertension within 5 years, and two-thirds progressed to hypertension within 10 years. Women with hypertension at baseline had the highest age-adjusted rate of cardiovascular events (4.32/1000 person-years) followed by women with high-normal BP (2.92/1000 person-years), compared with normotensive women (1.62/1000 person-years). Diastolic hypertension is more prevalent among younger patients, but for those older than 50, systolic hypertension is a better risk predictor of cardiovascular events.

Treatment of systolic hypertension in men and women reduces stroke, myocardial infarction, heart failure, and death. Lifestyle changes, such as low sodium diets, decrease BP in experimental and real-world settings. Strategies to delay the development of hypertension among women could have a significant public health benefit. Unfortunately, women are less likely to have controlled hypertension despite medication. During the 1990s, undiagnosed hypertension and poorly treated hypertension increased among women whereas hypertension among men decreased; these differences were not explained by age. Women’s cardiovascular health, by survey data, may be deteriorating compared with men’s health.

Inadequate Recognition of Hypertension in PMW

Inadequate recognition and control of hypertension remain major obstacles in reducing adverse cardiovascular outcomes for women. Among the 93,676 women enrolled in the WHI-OS, 32% were hypertensive though with no known cardiovascular disease. Of these, 52% were on antihypertensive medications, yet only 36% were at BP goal of less than 140/90 mm Hg. Among diabetic women only 21% of patients reached goal pressures. These results appear related to insufficient therapy, as the majority of women were only on 1 antihypertensive agent. Multi-drug therapy may be necessary to control hypertension as women age and should be combined with lifestyle modifications, such as a low-sodium diet and an exercise regimen.

Future Directions

Hypertension in PMW is a major medical problem. Further understanding of the basic mechanisms leading to hypertension in postmenopausal women may promote or guide more effective and rational choices of antihypertensive treatment. Future research should focus on strategies to increase public awareness of the association of hypertension with age among both women and men, including high risk minority groups, to educate about and improve adherence to lifestyle modifications and to implement evidence-based medical practice.

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Disclosures

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