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Postmenopausal Hypertension

Licy L. Yanes, M.D. and **Jane F. Reckelhoff, Ph.D.**
Women's Health Research Center, University of Mississippi Medical Center, Jackson, MS

Center of Excellence in Cardiovascular-Renal Research, University of Mississippi Medical Center, Jackson, MS

Departments of Physiology and Medicine, University of Mississippi Medical Center, Jackson, MS

Abstract

Cardiovascular disease is the leading cause of morbidity and mortality in postmenopausal women. Hypertension is a major risk factor for cardiovascular disease. The mechanisms responsible for postmenopausal hypertension have not been completely elucidated. However, various mechanisms have been implicated to play a role. For example, there is evidence that changes in estrogen/androgen ratios favoring increases in androgens, activation of the renin-angiotensin and endothelin systems, activation of the sympathetic nervous system, metabolic syndrome and obesity, inflammation, increased vasoconstrictor eicosanoids, and anxiety and depression may be important in the pathogenesis of postmenopausal hypertension. There is also evidence that hypertension is less well controlled in aging women than in aging men, but the reasons for this gender difference is not clear. Postmenopausal hypertension is likely multifactorial. Future studies will be necessary to determine the contribution of these systems listed above in mediating postmenopausal hypertension and to design treatment strategies that encompass these mechanisms to improve the quality of life of postmenopausal women as they age.

Keywords

androgens; estrogens; angiotensinogen; endothelin; leptin; 20-HETE; sympathetic activity

Cardiovascular disease is the leading cause of morbidity and mortality in men and women [1-10], but the incidence of cardiovascular disease-related deaths is higher in women than men [1,4-6]. Hypertension is one of the leading risk factors for cardiovascular disease [1,4,6,11]. Aging in both men and women is characterized by increases in blood pressure (BP) [1-10], but the age-related increases are more rapid in women than in men [6, 8-10], and the prevalence of hypertension in postmenopausal women is higher than in men [1,5-7,11]. In the world in general, 25% of adult women are hypertensive, and in the United States, more than 75% of women over 60 years of age are hypertensive [8,9]. In studies using the National Health and Nutrition Examination Survey (NHANES) 1999-2004 data set, the percentage of individuals with uncontrolled BP was 50.8 ± 2.1% in men and 55.9 ± 1.5% in women, although. women were more likely to have their BPs measured within the previous six months than men [11]. Despite this, comparison of the NHANES III cohort with the NHANES IV cohort showed that women were more likely to have poorly controlled hypertension than men, although the drugs to treat hypertension were similar between men

To whom correspondence should be sent: Jane F. Reckelhoff, Ph.D., Department of Physiology and Biophysics, University of Mississippi Medical Center, 2500 N. State Street, Jackson, MS 39216-4505, Telephone: 601-984-1819, FAX: 601-984-1817, JReckelhoff@umc.edu.

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and women [11]. Non-dipping of BP at night is associated with increased target organ damage [12-16]. However, there is evidence that non-dipping in women in general is associated with greater target organ damage than in men [12,16], and postmenopausal women are more likely than pre-menopausal women to exhibit nocturnal non-dipping of BP [12]. Thus while antihypertensive methods are similar between men and women and women are more likely to have their BPs measured, hypertension may be less well controlled in women. This suggests that perhaps the mechanisms responsible for hypertension in women may differ from the mechanisms in men.

The specific mechanisms responsible for the increased BP in women following menopause are not clear. Several physiological systems have been implicated in clinical studies. For example, postmenopausal women exhibit increases in plasma renin activity [17,18] and endothelin [19], compared to their premenopausal counterparts. Longitudinal studies have shown that serum androgen levels are increased in postmenopausal women, leading to alterations in estrogen/androgen ratios [20]. In addition, Ward and colleagues reported that hypertension in postmenopausal women, not age-matched men, was associated with elevated excretion of 20-HETE, vasoconstrictor eicosanoids [21]. Markers of oxidative stress are also increased in postmenopausal women [22-24], and oxidative stress has been shown to increase BP by reducing the bioavailability of nitric oxide [25]. The incidence of obesity may be as high as 40% in postmenopausal women [26], and increases in body weight have been shown to be associated with increases in BP [27]. Obesity is one component of the cluster of features known as the metabolic syndrome, that also includes insulin resistance, type II diabetes, hyperlipidemia, and hyperleptinemia, that could also impact BP [27]. Rossi and colleagues reported that improvement in endothelial dysfunction and inflammation seen in response to antihypertensive medications was attenuated in postmenopausal women, aged 47-60 years, who exhibited symptoms of the metabolic syndrome [28]. Thus the presence of metabolic syndrome not only may contribute to the hypertension but may affect response to treatment therapies in postmenopausal women.

Increased body weight, plasma leptin levels and aging have been shown to cause sympathetic activation [27,29,30]. Whether sympathetic activity is increased in postmenopausal women is not clear, however. Czarnecka and colleagues reported that the levels of norepinephrine and leptin were higher in postmenopausal women than age-matched premenopausal women [31]. However, Hogarth and colleagues found that both muscle sympathetic nerve activity (MSNA) and mulitunit bursts (b-MSNA were higher in age-matched normotensive and hypertensive men than normotensive and hypertensive women, respectively [32].

Chronic inflammation and increased levels of cytokines have been shown to contribute to hypertension in certain circumstances, such as in models of pre-eclampsia [33]. Although inflammation and inflammatory cytokines are elevated with menopause [34], the role that chronic inflammation may be play in mediating postmenopausal hypertension is not clear. In addition to having a direct effect on BP, inflammation may also be a consequence of lack of psychological well-being in these aging women.

In this review, we will discuss the evidence that each of these factors may contribute to postmenopausal hypertension and will develop a unifying hypothesis that incorporates them all. There is also a brief mention of the potential role that depression and psychological well-being may play in contributing to postmenopausal hypertension.

The aged female SHR as a model of postmenopausal hypertension

In the past several years we have characterized an animal model of postmenopausal hypertension, the aging female spontaneously hypertensive rat. When young, these females

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have significantly lower BPs than do their male counterparts (see Figure 1) [35]. With aging and cessation of estrus cycling (which occurs at 10-12 months of age), the BP increases in these females, such that by 16-18 months of age, their BPs are similar to or even higher than in age-matched males (see Figure 1). In addition, while serum estradiol levels are significantly reduced, serum androgens levels are elevated by 3-4 fold. Renal vascular resistance is also significantly elevated showing that the renal vasculature is constricted.

Most clinical studies to discern the mechanisms that could be responsible for postmenopausal hypertension in women have yielded correlative data, rather than mechanistic data because of the limitation against invasive techniques, expense and difficulty of obtaining longitudinal data. In addition, most studies using animal models to study potential mechanisms responsible for postmenopausal hypertension have employed young, ovariectomized animals that do not exhibit the age-related changes that are present in women as they make the menopausal transition. Furthermore, more and more studies including the studies of the Women's Health Initiative [36], HERS I and HERS II [37,38] have shown that hormone replacement therapy (HRT) in older individuals does not have the same beneficial cardiovascular effects as HRT in young women with premature ovarian failure [39]. Thus it is imperative that animal studies take into consideration the effect of aging and cessation of estrus cycling as models of postmenopausal hypertension. Therefore, as we discuss the potential mechanisms responsible for postmenopausal hypertension that have been implicated in women, we will also discuss studies we and others have performed in various animal models to test these hypotheses.

Potential Mechanisms responsible for postmenopausal hypertension

Role of changes in estrogen/androgen ratios in mediating postmenopausal hypertension

Whether the presence of estradiol protects against increases in BP in premenopausal women, and conversely, whether the lack of estradiol contributes to hypertension in postmenopausal women is controversial and unknown. For example, Olszanecka and colleagues measured ambulatory BP in normotensive and hypertensive women, aged 40-60 years, and found that BP was similar in normotensive and hypertensive groups regardless of presence or absence of menopause [40]. Unfortunately, there have been no studies to our knowledge in which ambulatory BP has been measured serially over the perimenopausal transition.

In experimental settings, many *in vitro*, estradiol has been shown to have a variety of effects that should be cardiovascular protective [41-43]. However, despite the potential of estradiol to protect against cardiovascular disease, large clinical trials on the effect of hormone replacement therapy (HRT) in post-menopausal women do not support these previous findings. The results of the Women's Health Initiative studies [36], and HERS I and HERS II [37,38] trials have not supported a role for HRT in prevention of either primary or secondary cardiovascular disease, respectively. Similarly, HRT has not been shown to consistently lower BP in post-menopausal women. As determined by 24 hr ambulatory BP monitoring, HRT typically results in changes of 3-5 mm Hg only [44-51]. In some studies, only daytime BP was reduced [45-47]; in others, only night time BP was reduced [48]. In some studies only systolic BP [47], in others only diastolic BPs [49,50], were reduced with HRT. The mode of delivery of HRT, whether oral or transdermal, and the dose, whether high or low, may play a role in its efficacy, but the data are not consistent with which delivery mode is more effective. These studies all looked at short-term effects of HRT on BP; i.e. less than one year. Ichikawa and colleagues did find that transdermal hormone therapy for 12 and 24 months did reduce diastolic and mean BP in normotensive postmenopausal women [52]. In contrast, Prelevic and colleagues studied healthy post-menopausal women who had been taking HRT for at least 5 yrs, and found that there was either no effect on BP or that BP was in fact higher in some women using HRT [53]. Proponents of the beneficial role of estradiol in

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cardiovascular disease cite the use of progesterone in HRT as possibly negating the positive effects of estradiol [41,54]. However, in women with surgical menopause and hysterectomy, estrogen replacement therapy (ERT), also did not result in significant sustained reductions in BP or reductions in cardiovascular disease risk [55]. Thus reductions in estradiol that occur at menopause do not fully explain the progressive increases in BP in postmenopausal women, and estrogen replacement is not used as an antihypertensive in their treatment.

However, there is evidence that loss of estrogens at any age contributes to endothelial dysfunction, which is common in individuals with hypertension. Taddei and colleagues reported that in response to acetylcholine, an index of endothelial dysfunction, endothelium-dependent flow mediated vasodilation (FMD) was less attenuated with age in menstrual cycling hypertensive women than men, but after menopause, the FMD response was attenuated to the same extent in both women and men [56]. Attenuated FMD is prognostic of coronary artery disease risk factors, including hypertension, in postmenopausal women [57]. Women with premature ovarian failure before age 40 years also exhibit reduced brachial FMD compared to age-matched cycling women, but in these women, HRT with conjugated equine estrogen and medroxyprogesterone for 6 months reversed the endothelial dysfunction [55]. In contrast, in the Women's Angiographic Vitamin and Estradiol (WAVE) Trial, HRT had no beneficial effect on FMD in postmenopausal women [58]. The fact that HRT protected against endothelial dysfunction in young women, but not in older women, both of whom had experienced menopause, supports the contention that aging may change the response to HRT and thus may independently contribute to increases in BP.

Endothelial dysfunction is typically characterized by reductions in nitric oxide (NO). Estradiol stimulates NO production since estradiol acutely increases intracellular calcium which activates endothelial NO synthase (eNOS) [59]. In addition, estradiol upregulates synthesis of eNOS which would promote vasodilation and thus reductions in BP [41]. Estradiol also upregulates superoxide dismutase [60], which removes superoxide and reduces oxidative stress. Superoxide binds to NO and renders NO unavailable for vasodilation [25]. An intact NO system is necessary for antioxidants to reduce BP, however [61]. So in situations of chronic hypertension when endothelial dysfunction is present and NO levels have been reduced for long periods, estradiol may not be able to reduce BP, just as other antioxidants are not. Furthermore, we have not been able to show that oxidative stress contributes to the control of BP in female hypertensive animals as it does in male animals [62-64], suggesting that oxidative stress may not be a factor in mediating hypertension in women either. This could explain why clinical trials with antioxidants have not be successful in reducing BP [65]; e.g. the studies were not powered to separate women from men, and hypertension in women may be resistant to antioxidants.

Reductions in estradiol with menopause could affect the RAS. Animal studies have shown that estradiol downregulates the levels of angiotensin type I (AT1) receptors and angiotensin converting enzyme (ACE) levels [66,67], thus protecting against the activation of the renin-angiotensin system (RAS) and subsequent vasoconstriction. Therefore, reductions in estradiol would tend to activate the RAS. However, in normotensive postmenopausal women, HRT with transdermal 17β-estradiol and oral medroxyprogesterone reduced BP but had no effect on levels or expression of RAS components, including plasma renin activity, angiotensin I or II, aldosterone or angiotensin converting enzyme activity [52]. Expression of AT1 receptors were not measured in this study. In contrast, treatment of postmenopausal women with AT1 receptor antagonists did improve endothelial dysfunction measured by FMD, whereas a calcium channel blocker did not [68], supporting a role for the RAS in contributing to postmenopausal hypertension. This possibility will be discussed in more detail later.

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How androgens contribute to hypertension in postmenopausal women is also not clear. Studies in the Rancho Bernardo cohort in which serial androgen levels were measured showed that immediately following menopause, androgen levels are reduced, but that by 70 years of age, androgen levels are increased to levels found in premenopausal women [69]. The ovary in postmenopausal women is a major source of androgen production [70,71], but increasing evidence supports local production of androgens, such as by the kidney [72]. In men reduced levels of androgens are associated with cardiovascular disease [73-75]. This is not the case in women in which elevated levels of androgens are associated with cardiovascular abnormalities. Young women with polycystic ovary syndrome (PCOS) who have elevated levels of plasma androgens and normal plasma estradiol levels have increased risk of cardiovascular disease not only when young but also following menopause [76,77]. Thus the levels of androgens are indicative of differences in cardiovascular disease risk depending on gender, increased androgens predict cardiovascular disease in women; decreased androgen levels predict cardiovascular disease in men. Clinical studies have also shown that serum androgen levels increase with increasing body mass index in postmenopausal women, not premenopausal women [78]. This is different than in men in which decreases in androgens are associated with increases in body mass index and obesity [74,75]. In addition, elevated serum testosterone is associated with a higher risk of type II diabetes in postmenopausal women, but not age-matched men [79]. Other mechanisms by which androgens could increase BP in postmenopausal women will be discussed in the context of the effect of androgens on other pro-hypertensive systems below.

Changes in estradiol receptors with aging and menopause

The lack of positive results in the WHI [35] and HERS I and II [36,37] trials with hormone replacement therapy and prevention of primary or secondary coronary artery disease suggest that aging may cause changes in estradiol and its mechanisms of biological activity. For example, a study in aging men and women in which estrogen receptor alpha (ERα) localization was determined by immunohistochemistry in biopsy samples from hypothalami, found that ERα was found mainly in the cellular cytosol in postmenopausal women, but in hypothalamic nuclei in age-matched men and premenopausal women [80]. Longitudinal studies in female rats in which 17β-estradiol was replaced following ovariectomy at a young age, failed to maintain lower BP at 12 months of age compared to the levels that were attained at 4 months of age [81]. Data is woefully missing with regard to how estradiol receptor expression changes in tissues important in BP control with aging in males or females. Furthermore, there are no studies to address to whether intracellular signaling of estradiol and its receptors, ERα, ERβ, and the plasma membrane-associated ER, GPR30, may change with aging.

Role of obesity and metabolic syndrome in postmenopausal hypertension

Obesity is rapidly becoming an epidemic in all of the developed countries in the world. In the United States, the incidence of obesity is increasing in individuals in all states with the highest incidence existing in the southeast [82,83]. There are also ethnic differences in the incidence of obesity in the US. For example, 23.3% of non-Hispanic white women were found to be obese whereas 41.9% of non-Hispanic women were found to be obese [82]. Obesity has been shown to increase after surgical menopause and to be increased in women who started HRT within 12 months of amenorrhea [84]. These investigators also found that the incidence of obesity in women is associated with increases in free androgen index and reductions in sex hormone binding globulin. There is also evidence that even if women do not gain additional weight after menopause, there is a redistribution of body fat favoring an increase in abdominal fat gain rather than lower hip weight gain [85]. Weight that accumulates in the abdominal area is associated with a higher incidence of cardiovascular disease than weight that is accumulated in the lower body [86].

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The mechanisms by which weight gain or obesity cause hypertension are not clear. Increased body weight due to increased fat feeding in dogs increases BP that is prevented if the renal nerves have been severed [87], suggesting a sympathetic nervous system influence on the increase in BP with weight gain. Obesity is associated with increases in plasma leptin [27], and infusion of leptin increases BP in animals. Blockade of the sympathetic nervous system prevents this hypertensive effect [27]. Leptin has been shown to activate the sympathetic nervous system via activation of melanocortin (MC) 4 receptors in the hypothalamus [27,30]. Blockade of these receptors reduces BP in obese rats. Leptin has been shown to be increased in hypertensive postmenopausal women [40], and sympathetic activity has been shown to be higher in postmenopausal women than premenpausal women [31], but may be lower than in age-matched men [32].

Whether body weight alone or the combination of obesity and parameters of the metabolic syndrome, such as insulin resistance, hyperglycemia, hyperlipidemia, and hypertriglyceridemia, increase the risk of cardiovascular and renal disease and contribute to increased BP as well is controversial. Comparison of data from the Framingham Offspring, Atherosclerosis Risk in Communities, and Cardiovascular Health cohorts over more than 8 years, showed that abdominal obesity alone in these cohorts was not significantly associated with increased risk (odds ratio) of cardiovascular disease [88]. However, inclusion of 1-2 parameters of metabolic syndrome and diabetes did significantly increase the odds ratio of contracting cardiovascular disease in both men and women, suggesting that the presence of metabolic abnormalities and diabetes are more indicative of cardiovascular disease risk than abdominal obesity alone.

Role of the renin-angiotensin system (RAS) in mediating postmenopausal hypertension

A major system for controlling BP and body fluid volume (i.e. pressure-natriuresis) is the renin-angiotensin system [89,90]. Angiotensin II (Ang II) increases proximal sodium reabsorption by the kidney by stimulating epithelial transport [89,90]. Thus the renin-angiotensin system monitors the levels of sodium and body fluid volume and adjusts its levels according. However, when Ang II levels are too high for the existing volume in the body, hypertension occurs [91]. Similarly, if the body fluid volumes are perceived incorrectly, hypertension will occur. BP in women has been shown to be more salt-sensitive as they age than in men [92]. Thus it is possible that there may be a blunting of the renin response to changes in salt in postmenopausal women. There may also be a genetic component of the RAS that contributes to postmenopausal hypertension since certain renin gene polymorphisms are associated with hypertension in women, aged 40-70 years, but not in men [93].

With regard to therapeutics, women may respond differently than men to blockade of the RAS. Miller and colleagues reported that while irbesartan, the AT1 receptor antagonist, reduced BP in both men and women, women developed Ang II insensitivity at a lower dose than did men, despite the fact that the levels of AT1 receptor expression in skin (by real time RT-PCR) was not different in men and women [94]. In addition, Canzanello and colleagues found that non-Hispanic white ethnicity, female gender, higher plasma renin activity and lower body weight predicted a greater response to candesartan [95]. Therefore, one reason for the lack of BP control in postmenopausal women, described previously [11], may be due to differential responses to drug therapy, including RAS blockers

Androgens can contribute to activation of the RAS by increasing intrarenal angiotensinogen [96,97,98]. An increase in renin substrate could contribute to activation of the RAS if renin is not working at its enzymatic Vmax, which has not been studied in postmenopausal women, to our knowledge. In addition, animal studies support the notion that obesity and increases in leptin are associated with activation of the RAS [99]. Thus

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postmenopausal increases in androgens and body weight could also activate the RAS leading to hypertension. As mentioned previously, the reduction in estrogens would also upregulate the AT1 receptor expression and ACE activity [41-43]. Ovariectomy of animals is known to increase body weight, thus also creating the link between loss of estrogens, weight gain and activation of the RAS. In our postmenopausal hypertensive rats, while losartan, the AT1 receptor antagonist, decreased BP, it was not normalized [100], suggesting that RAS activation was not the only contributor to the postmenopausal increases in their BP.

Role of endothelin in postmenopausal hypertension

Chronic infusion of Ang II has been shown to stimulate synthesis of preproendothelin [101], another potent vasoconstrictor. When given chronically, endothelin causes increases in sodium reabsorption in the kidney and increases BP [102,103]. Endothelin could also play a role in increasing BP by contributing to oxidative stress. In postmenopausal women, plasma endothelin levels have been shown to be increased [104], suggesting that endothelin may play a role in the increased BP following menopause. The biological activity of endothelin is mediated by two receptors, the ET_A and ET_B receptors. The majority of the vasoconstrictor action of endothelin is thought to be mediated via the ET_A receptors [105]. ET_B receptors are thought to be coupled to nitric oxide, and when blocked, cause an increase in BP in Ang II-treated rats [106]. These data support our contention that endothelin may contribute to the increased BP in postmenopausal rats and women. Whether there are changes in endothelin receptors in postmenopausal women has not been studied to our knowledge.

The mechanism by which endothelin itself increases in postmenopausal women is alo not clear. Endothelin synthesis can be upregulated by Ang II, as mentioned above [101], and ET_A receptors have been shown to mediate Ang II hypertension [105,107]. Furthermore, in women who have PCOS, which is characterized by hyperandrogenemia and increased plasma renin activity, plasma endothelin is also increased [108]. The role played by estradiol in endothelin levels is controversial. While postmenopausal women have been shown to have elevated levels of endothelin, hormone replacement therapy with either micronized 17β-estradiol and didrogesterone or conjugated equine estrogen and medroxyprogeterone both increase endothelin levels in postmenopausal women [109]. Elevated androgen levels that occur with menopause and aging could also increase endothelin levels. Studies in transsexual individuals who receive androgens for masculinization have been shown to have increased plasma endothelin levels [110]. In contrast, activation of the RAS caused by androgen-mediated increases in angiotensinogen [97,98] could also lead to increases in endothelin since angiotensin II stimulates endothelial synthesis [101]. Increased endothelin is also a factor in endothelial dysfunction that occurs with aging.

Studies in our postmenopausal rat model show that endothelin peptide levels are higher than in young controls and that blockade of the endothelin ET_A receptor reduces their BP, but has no effect on BP in young female SHR or in age-matched old males [111]. However, just as with RAS antagonists alone, ET_A receptor antagonists alone failed to normalize the BP in these old females, again suggesting that a combination of factors contribute to the hypertension in postcycling old female SHR.

Role of inflammation in mediating postmenopausal hypertension

Menopause is associated with increases in C-reactive protein (CRP), an indicator of inflammation, and CRP levels have been shown to predict negative cardiovascular outcomes in postmenopausal women who use HRT and those who do not [112,113]. Chronic inflammation, defined as increases in tumor necrosis factor- alpha (TNF-α) and inflammatory interleukins (IL), such as IL-6, is also a common finding in obese postmenopausal women [114]. In fact, longitudinal studies in women as they transitioned from

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pre- to postmenopausal status showed that increases in inflammatory markers were mainly due to increases in visceral adiposity in the women [115].

Inflammation has been shown to increase BP in various models. For example, angiotensin II hypertension is attenuated in IL-6 knockout mice [116], suggesting that inflammation could contribute to hypertension in postmenopausal women who have activated RAS. Chronic inflammation is also a common finding in women with hyperandrogenism and PCOS, as measured by increases in C-reactive protein, TNF-α and IL-6. Tarkun and colleagues reported that the elevated levels of TNF-α and IL-6 correlated well with insulin resistance and hyperglycemia in women with PCOS [117], suggesting that androgens may increase inflammation. However, why TNF-α is increased with hyperandrogenemia in females is not clear, since in males, androgens are anti-inflammatory [118,119]. Treatment of obese men with androgens causes a reduction in inflammatory cytokines [119]. TNF-α has been shown to increase BP in some but not all circumstances. LaMarca and colleagues reported that TNF-α infusion in ovariectomized normotensive female rats replete with estradiol or progesterone did not increase their BP [120]. Similar findings were made in normal pregnant female rats. However, in pregnant rats in which TNF-α is increased, such as the model of reduced uterine perfusion pressure (RUPP) that is hypertensive, etanercept, the TNF-α soluble receptor, significantly reduced BP [121].

Role of Eicosanoids in mediating postmenopausal hypertension

Arachidonic acid is converted to epoxyeicosotetraenoic acids (EETs) by epoxygenases or to 20-HETE by omega-hydroxylases. Ward and colleagues found that urinary excretion of 20-HETE, a vasoconstrictor, is higher in hypertensive women with endothelia dysfunction than in age-matched men [21]. Androgens are known to increase the synthesis of 20-HETE via their effect on the synthesis of some of the subtypes of the omega-hydroxylases, that leads to hypertension [122,123]. Wu and colleagues have also recently shown that androgen-mediated increases in 20-HETE activate NF-κB and increase BP which is prevented by blockade of both 20-HETE synthesis and IκB kinase inhibitors [124]. We have preliminary data in our rat model of postmenopausal hypertension that suggest that 20-HETE may contribute to their hypertension. EETs are vasodilators that may be decreased following menopause, and thus contribute to postmenopausal hypertension. Future studies are necessary to follow up on these observations and hypotheses.

Role of anxiety and depression in mediating postmenopausal hypertension

Anxiety and depression may contribute to hypertension or women who are hypertensive may exhibit a higher rate of anxiety and depression. Depression and anxiety occurs at a significantly higher rate in women than in men [125]. Depression and anxiety also are associated with increased risk of cardiovascular disease. For example, individuals with bipolar disorder have an increased risk of hypertension [126]. Sympathetic activity can be increased with anxiety and chronic mental stress leading to increased BP, and this has been shown to be relevant in individuals with metabolic syndrome and hypertension [127]. Sustained hypertension was also found to be associated with increased level of anxiety in a small Spanish cohort [128]. Furthermore, ACE inhibitors used for the treatment of hypertension were found to reduce the occurrence of depression with anxiety [129]. The mechanisms by which chronic anxiety and depression cause hypertension and may contribute to postmenopausal increases in BP are not clear and should be studied further.

Summary

In summary, the mechanisms responsible for postmenopausal hypertension are likely multifactorial. As shown in Figure 2, we hypothesize that changes in estrogen/androgen

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ratios that favor increases in androgens lead to activation of the RAS. Increases in androgens and Ang II can increase endothelin levels, and both Ang II and endothelin increase ω-hydroxylase activity (and 20-HETE synthesis) by increasing release of arachidonic acid from plasma membranes. Androgens promote synthesis of subtypes of ω-hydroxylases, such as cytochrome P450 4A2 and 4A8, in the vasculature. In combination with Ang II and endothelin, this leads to increases in vascular 20-HETE. In addition, we hypothesize that the increases in androgens with aging in postmenopausal women lead to increases in food intake and visceral adiposity leading to increases in leptin which in turn activate the sympathetic nervous system via the MC 4 receptors in the hypothalamus. Sympathetic activation would also increase intrarenal renin release and thereby also contribute to increases in Ang II. We further hypothesize that the combination of reductions in estrogens, increases in androgens, increases in visceral adiposity and increases in Ang II lead to increases in inflammatory cytokines, such as TNF-alpha, mainly via activation of NF-κB. The combination of increases in TNF-alpha, sympathetic activity, Ang II, endothelin and 20-HETE all lead to increases in renal vascular resistance and hypertension. We believe that hypertension may be controlled differently in postmenopausal women than age-matched men. Thus future studies are necessary to delineate the mechanisms responsible for postmenopausal hypertension and to develop treatment options specific for these women.

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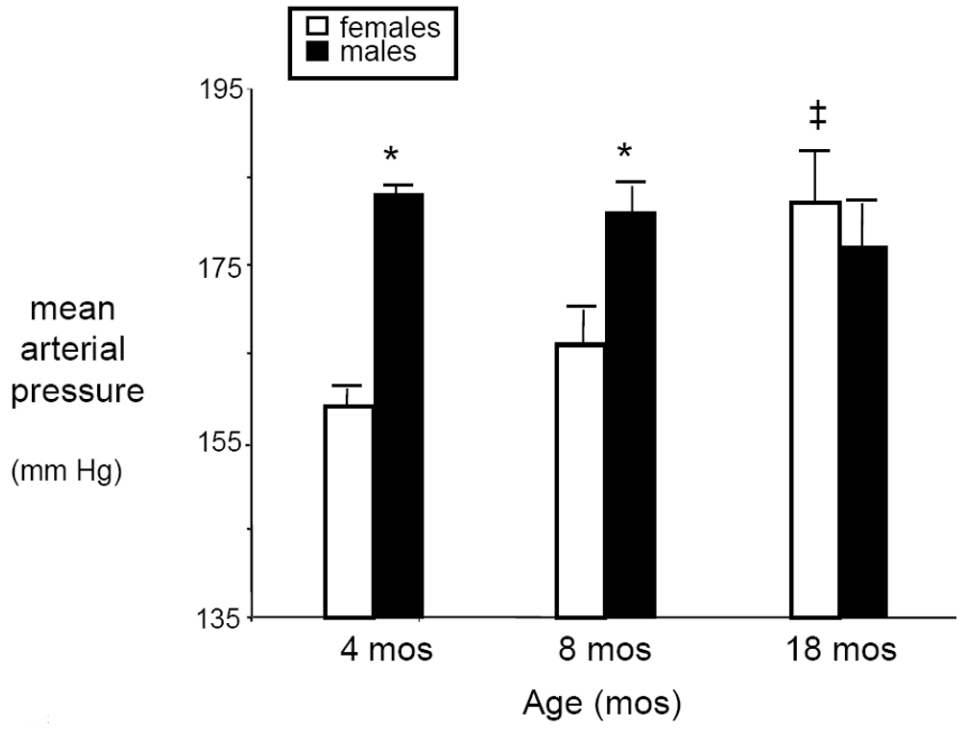

Figure 1. BPs in male and female spontaneously hypertensive rats with aging

*, $p<0.05$, males compared with females, aged 4 and 8 months; ‡, $p<0.05$, females compared to females, aged 4 and 8 months.

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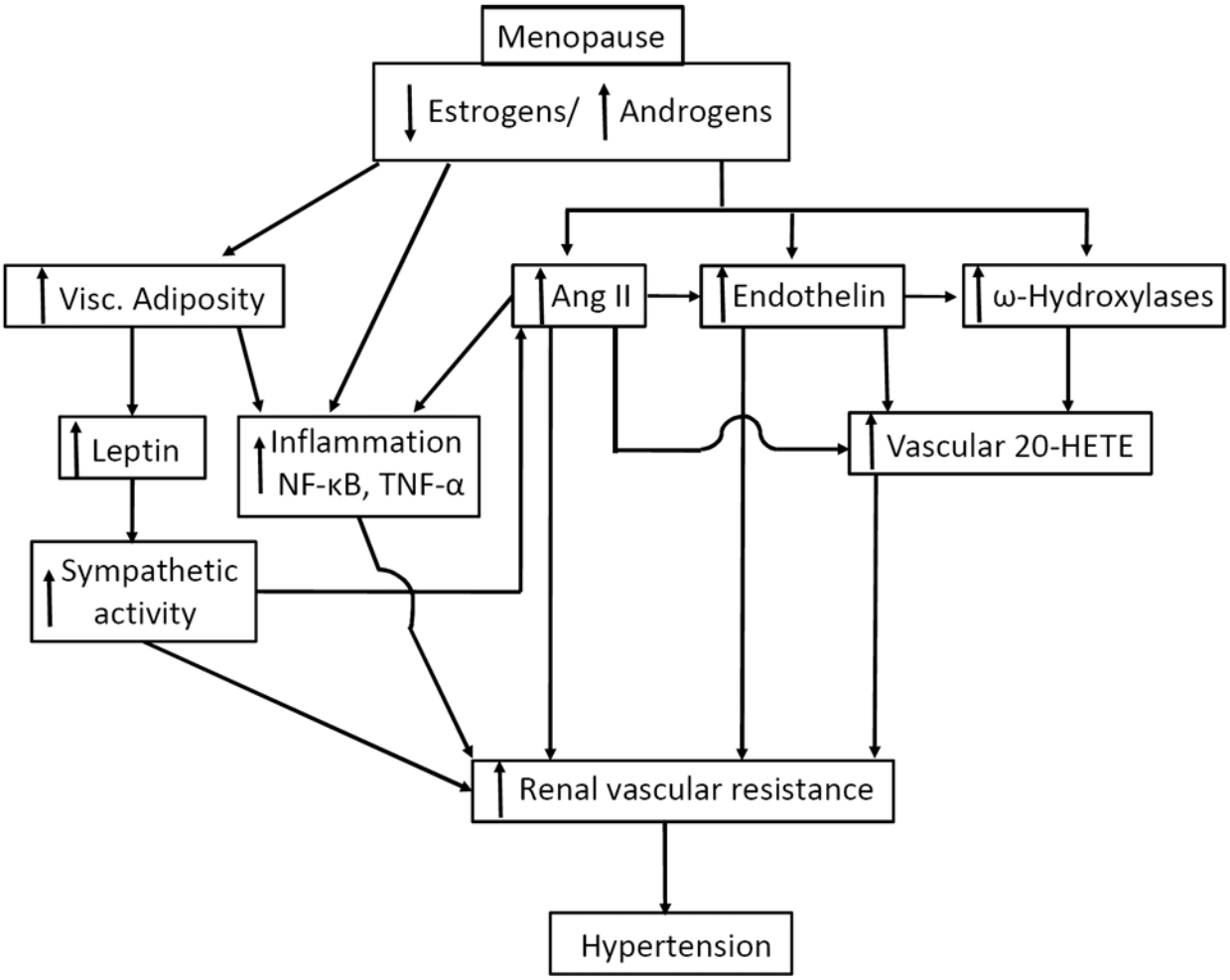

Figure 2. Schematic of potential mechanisms contributing to postmenopausal hypertension
Abbreviations: Ang II, angiotensin II; Visc, visceral; TNF-α, tumor necrosis factor-alpha; 20-HETE, 20-hydroxyeicosatetraenoic acids.