JMM
pISSN: 2288-6478, eISSN: 2288-6761
http://dx.doi.org/10.6118/jmm.2014.20.1.1
Journal of Menopausal Medicine 2014;20:1-6

Review Article

Postmenopausal Hypertension and Sodium Sensitivity

Jun-Mo Kim, M.D., Ph.D.[1], Tae-Hee Kim, M.D., Ph.D.[2], Hae-Hyeog Lee, M.D., Ph.D.[2], Seung Hun Lee, M.D., Ph.D.[3], Tong Wang, M.D., Ph.D.[4]

Departments of [1]Urology and [2]Obstetrics and Gynecology, Soonchunhyang University, College of Medicine, Bucheon, Korea, Departments of [3]Nephrology and [4]Cellular and Molecular Physiology, Yale University, School of Medicine, New Haven, USA

It has been well established that women generally have lower incidence rates of hypertension than men at similar ages and these differences may vary with age. It also has been observed in many studies that after menopause, blood pressure (BP) increases in women to levels even higher than in men. The lack of estrogens may not be suggested as the only component involved in the development of postmenopausal hypertension. Thus, in this mini-review, the possible mechanisms by which sex hormones may influence the BP are discussed. This review also examines the renal regulatory mechanisms for gender differences in BP and explores the effects of salt intake on BP (salt-sensitivity) in pre and post-menopausal women.
Estrogen has been shown to stimulate nitric oxide (NO) production, thus female sex hormones have a beneficial effect on BP control. Evidences that angiotensin type 2 receptor (AT_2R) is up-regulated by estrogen support the favorable effects on BPs in women than men. The kidney plays an integral role in the regulation of arterial pressure through the mechanism of pressure-natriuresis, which has been shown to be modulated by the RAS. The prevalence of salt-sensitivity increases with age and low-salt diets has shown to help reduce systolic BP (SBP) and diastolic BP. While oral hormone replacement therapy has yielded only a neutral or minimal effect on the elevation of SBP, both the transdermal route replacement and a novel progestin with anti-aldosterone activity (drospirenone) has also shown to reduce SBP. **(J Menopausal Med 2014;20:1-6)**

Key Words: Blood pressure, Gender difference, Hypertension, Postmenopause, Sodium excretion

Introduction

It has been reported that blood pressure (BP) increases with advancing age, and the prevalence of hypertension also increases with age in both men and women equally. However, the features of hypertension are different in both sexes and thus has been studied extensively. The epidemiologic study on prevalence of hypertension in Korean adults supports this gender difference.[1] In this study, hypertension was defined by World Health Organization (WHO) criteria;− a systolic BP (SBP) ≥ 140 mmHg and diastolic BP (DBP) ≥ 90 mmHg.[1] The prevalence of untreated isolated systolic hypertension and untreated systolic/diastolic hypertension (SDH) was the higher in women over 70 years of age (18.25% and 12.36% respectively) than age−matched men (15.81% and 18.25% respectively).[1] The prevalence of untreated SDH in women has also consistently been 4% lower than men in all age groups less than 70 years. Their study has also shown that the prevalence of untreated SDH had increased more than two−fold from premenopausal women (5.06% in their forties) to postmenopause (10.72−12.36% in the over fifty age group).[1] Of note, gradual increase in BP after menopause take an average of 5 to 20 years to develop, which suggests the important role of female sex hormones on regulation of BP.[2] The renin−angiotensin−aldosterone system (RAAS)

Received: March 3, 2014 **Revised:** March 20, 2014 **Accepted:** March 20, 2014
Address for Correspondence: Tong Wang, Department of Cellular and Molecular Physiology, Yale University, School of Medicine, 333 Cedar St, New Haven, CT, USA 06520−8026
Tel: +1−203−785−4074, Fax: +1−203−785−4951, E−mail: tong.wang@yale.edu

has a major role in regulation of BP and renal excretion of sodium. The regulation between BP and renal excretion of sodium can be expressed in terms of a pressure-natriuresis relationship. Pressure-naturiuresis is precisely modulated by two key regulators, Angiotensin II (Ang II) and nitric oxide (NO).[3] Whereas Ang II in RAAS promotes an augmented BP, NO, which is a very short-lived vasodilator, decreases BP.[4] Estrogen could up-regulate NO production rapidly and progesterone has an anti-mineralocorticoid effect.[5,6] In this mini-review, we discuss the pressure-natriuresis control mechanisms, focusing on interaction among Ang II, NO and estrogens as well as salt sensitivity and gender differences of BP control mechanisms mainly based on angiotensin receptors and endothelin receptors. We discuss the change of control mechanism of BP and sodium excretion in pre- and postmenopausal states.

Renal Regulatory Mechanisms of BP and Sodium Excretion

1. Pressure-Natriuresis Relationship

Pressure-natriuresis refers to the relationship between sodium excretion and mean arterial pressure, when increased arterial pressure which elicits an increase in sodium excretion and a decreased in extracellular fluid (ECF) volume. It therefore results in a decreased venous return, cardiac output, and finally reduces BP (Fig. 1A).[2] Ang II induces elevated BP due to vasoconstriction, as well as an increase of sodium absorption in kidney tubules, rather than decreasing glomerular filtration rate (GFR). Ang II can increase GFR by contraction of the efferent arteriole, since the pressure difference between the afferent and efferent arterioles increases, creating greater filtration pressure. This function has an important role in preventing a decreased GFR during volume depletion.[7] However, long-term hypertension and prolonged Ang II production shifts natriuresis right in the relationship curve and results in a reduction in renal excretory function (Fig. 1B). This is because higher intrarenal Ang II can upregulate ion transporters activity as well as the transporter expression such as the Na/H-exchanger in the proximal tubule and Na/Cl^--cotransporter in the distal convoluted tubule.[8,9] A decreased renal sodium excretion or rightward shift of this curve can lead to an elevated BP and the development of hypertension by ECF expansion.[10] It has been suggested that sex hormones may regulatethe pressure-natriuresis function, according to a reports, the pressure-natriuresis was blunting in male spontaneously hypertensive rat (SHR), testosterone treated, and ovariectomized female rats. In contrast, castration of male SHRs restores the bunted pressure-natriuresis relationship.[11]

2. Gender Differences in Pressure-Natriuresis Relationship and Angiotensin Receptors

Previous studies have shown that gender differences in the pressure-natriuresis relationship and in RAAS are caused by functional difference between male and female sex hormones. A study demonstrated that plasma renin activity (PRA) is positively modulated by androgens and

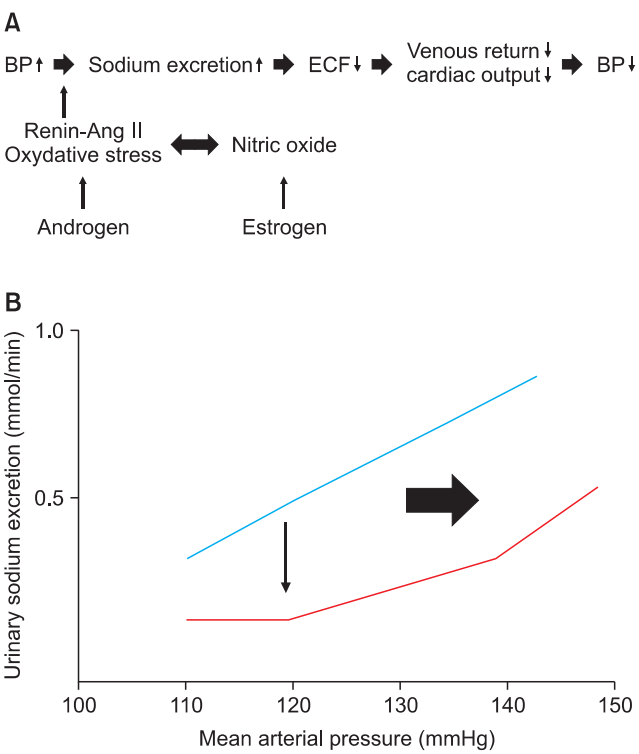

Fig. 1. (A) Renal major regulatory mechanism of blood pressure (BP) and sodium excretion. Increased BP induces sodium excretion via pressure-natriuresis relationship, and angiotensin II (Ang II) and nitric oxide (NO) modulate this relationship. Female and male sex hormones affect this process via the regulation of renin- Ang II and NO. (B) Pressure-natriuresis relationship. If it shifts rightward, the amount of sodium excretion will decrease in the same mean arterial pressure. (ECF: extracellular fluid, BP: blood pressure)

 http://dx.doi.org/10.6118/jmm.2014.20.1.1

antagonized by estrogens via an increase in NO generation.[12] Therefore, prorenin and PRA levels are greater in men than in women. James et al.[13] reported that PRA was 27% higher in men than in women in all age groups. In some female cases, elevated PRA levels were associated with diabetics (21.2 mU/L vs 13.5 mU/L) under conditions without estrogen replacement therapy (13.2 mU/L vs 10.9 mU/L).[14] Experimental data show that the level of serum testosterone yielded a linear correlation with PRA in Sprague-Dawley rats.[2] These results suggest that better BP control using an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) can be achieved in male than female. Reckelhoff et al.[15] demonstrated that Enalapril decreased BP by 65% in male SHRs which was greater than in female rats (40%). Nonetheless, gender differences in the efficacy of ACE inhibitor and ARB have rarely been demonstrated in clinical studies. Although meta-analysis from Rabi et al.[16] found a small but better response in men than women, this gender difference in effect was much smaller than the benefit from treatment with these agents in women. The different expression of subtype of Ang II receptor (AT)-Ang II type 1 receptor (AT1R) and Ang II type 2 receptor (AT2R) between two sexes seems to play a partial role in gender differences on the effect of ACE inhibitors or ARB. Because AT1R is the predominant AT receptor in both men and women, most ARB agents used clinically, including losartan, are AT1R antagonists. However, Ang II also activate AT2R and the function of AT2R is counter-regulation of BP and sodium absorption in the proximal tubule.[17] Activation of the AT1 receptor increases BP as well as sodium absorption, whereas activation of AT2 receptor reduces BP and Na absorption in the proximal tubule.[18] It has been reported that AT2R expression is higher in female than male rats.[19] Hilliard et al.[20] demonstrated that AT2R blockades the blunted pressure-natriuresis relationship and resulted in a rightward shift of the curve in both males and females; this effect is likely due to increased Na^+ absorption in proximal tubules by AT2 blocker as we demonstrated previously.[17]

3. Gender Differences in Endothelial Function-NO and Endothelin (ET) Receptor

NO down-regulate the expression of AT1R and antagonize Ang II production.[12] As mentioned earlier, estrogen exert stimulatory effects on both endothelial NO synthase (eNOS) activity and NO generation.[12] Whole-body production of NO in healthy premenopausal women (mean 2111 nmoL of urinary 15 N nitrate excretion) was greater than in healthy young men (mean 1682 nmoL).[21] As female hormones have beneficial effects in preventing development of hypertension and cardiovascular disease, a reduction of GFR according to advancing age is also delayed and attenuated in women (0.8 mL/min/1.73 m^2 per estimated GFR) compared to men (1.4 mL/min/1.73 m^2 per estimated GFR).[22] Furthermore, the progression of acute renal injury and chronic renal disease is slower in women than men.[12,23] These findings are related to gender differences of ET activity. ET-1 is well known as not only the most potent long-lasting vasoconstrictor known to date but also a potent pro-inflammatory agent.[24,25] It was found that the ET-1 levels are higher in men (mean 5.9 pg/mL) than in age-matched women (mean 4.1 pg/mL) and lower in pregnant women in age-matched compared to non-pregnant controls.[26] The crosstalk between ET, Ang II, NO and oxygen free radicals has been investigated intensively. Elevated level of ET-1 increased renal vascular resistance by 37% and reduced sodium excretion by 36% consistent with its vasoconstriction and sodium retention effect in human.[27] Two ET receptors have been cloned, ET_A and ET_B, the ET_A receptor, which preferentially binds ET-1 and the ET_B receptor, which equally binds ET-1 and ET-3.[28] ET_B receptor engender vasodilatation and natriuresis via NO production on endothelial and tubular cells.[29,30] Therefore, ET_B receptors provide a protective mechanism against elevated BP. Females have increased ET_B function and perhaps reduced ET_A effects, and it has a role as one of physiologic mechanisms of reduced BP in women.

Menopause and Salt Sensitivity

1. Salt Sensitivity and Female Sex Hormone

Because female sex hormones affect renal sodium excretion as well as BP control, spontaneous free sodium intake appears to be greater in females than in males in many mammals.[31] This difference may originate in the need to preserve sodium losses during pregnancy.[31] Loss

of female sex hormones affect the pressure-natriuresis relationship curve, (it shifted to the right), which indicates how one may become salt sensitive after menopause.[32] Kawasaki et al.[33] have first used the terms salt-sensitivity and salt-resistant. They classified the subjects who showed an increase BP greater than 10 mmHg at the end of a high-salt diet rather than a normal-salt diet as 'salt-sensitivity'.[33] In contrast, the term of 'salt-resistant' was used in subjects who showed an increase in BP <5 mmHg.[33,34] The renal hemodynamic response is different in salt-sensitive and resistant subjects (Fig. 2). Salt loading during the luteal phase in premenopausal women (progesterone and secondary estrogen surge) resulted in renal vasodilatation and reduced filtration faction, which is the ratio of the GFR to the renal plasma flow (RPF), with no change in GFR.[35] In contrast, salt-sensitive postmenopausal women showed reduced GFR and an increase in the filtration fraction.[31] Endogenous estrogen may modulate this mechanism by increasing NO bioavailability and decreasing the AT1/AT2 receptor ratio.[3]

2. Salt-Sensitivity and Menopause

Clinical studies have shown that the prevalence of salt sensitivity increases with age and is higher in hypertensive women than normotensive women. The mean age of the normotensive sodium-sensitive group (35.3 years) was older than the resistant group (26.9 years) and the hypertensive sodium-sensitive group (43.8 years) was older than resistant group (35.5 years).[32] In the same study, higher salt sensitivity was identified in more hypertensives (>50%) than normotensives (25%).[32] Tominaga et al.[36] also demonstrated that female sex hormone level in hypertensive postmenopausal women were significantly lower than normotensive age-matched women. Further, salt sensitivity was observed in 66.6% (8/12 subjects) in hypertensive patients and 14.2% (1/7) in normotensive women.

3. Treatment of Hypertension and Salt-sensitivity in Postmenopausal Women

Even though WHO guideline recommend salt consumption of 2 g/day, salt consumption in Korea and many countries is two times greater than the recommended value. The efficacy of a low-salt diet on decreased BP in salt-sensitive women depends on the amount of salt restriction. In recent meta-analyses on the effect of lower sodium intake on BP, when sodium intake was < 2 g/day, SBP and DBP were reduced by 3.47 mmHg and 1.81 mmHg.[37] This effect has also been demonstrated in children (0.84 mmHg and 0.87 mmHg respectively) and there were no adverse effects on blood lipids, catecholamine levels or renal function. However, caution should be applied in that low salt diets as non-pharmacologic therapy of hypertension are difficult to maintain over the long term.[38] Of note, because women become salt sensitive after menopause, the use of diuretics in hypertensive women is strongly encouraged.[39]

4. Hormone Replacement Therapy (HRT) and Anti-hypertensive Effects

Although endogenous estrogen has beneficial effects on sodium and BP regulation via NO production and RAAS, conflicting results have been reported in many clinical trials of HRT in postmenopausal women. Oral administration of estrogen has produced a neutral effect or a small increase in BP. In this placebo controlled trial of HRT, the estrogen plus progestin increased SBP (average < 2 mmHg), but not DBP.[39,40] In contrast, transdermal estrogen replacement was associated with a 4.2 mmHg reduction of mean nighttime SBP after 6 months.[41] The mechanisms for the different effects between the oral and transdermal route have not yet been elucidated.[39] A novel progesterone with an anti-aldosterone effect, Dropirenone 2 mg and 3 mg in combination with Estradiol reduced SBP by 6.1 mmHg and 4.7 mmHg, respectively.[42]

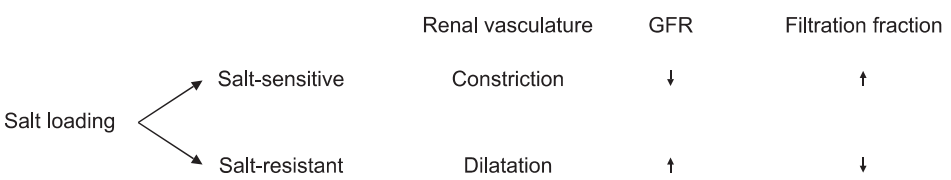

Fig. 2. Different renal response between salt-sensitive and salt-resistant subjects. Glomerular filtration rate is maintained after salt loading in salt-resistant subjects. The rate decreases in salt-senitive subjects. (GFR, glomerular filtration rate)

 http://dx.doi.org/10.6118/jmm.2014.20.1.1

Conclusions

Renin-Ang II and NO are two main counter-regulators modulating BP as well as sodium reabsorption and excretion. Estrogen affects this regulatory mechanism via up-regulation of NO production and different expression level of angiotensin receptors and ET receptors. These beneficial effects of estrogen would be lost after menopause, many women become salt-sensitive. Although a low-salt diet and conventional HRT is theoretically beneficial for the treatment of hypertension in salt-sensitive menopausal women, it has not yet been proven in clinical studies. The add-on therapy of diuretics is good option in such patients.

Acknowledgement

This work was supported by the Soonchunhyang University Research Fund.

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