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Sex and Gender Differences in Control of Blood Pressure

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Abstract

In recent years the interest in studying the impact of sex steroids and gender on the regulation of blood pressure and cardiovascular disease has been growing. Women are protected from most cardiovascular events compared to men, until after menopause, and postmenopausal women are at increased risk of cardiovascular complications compared to premenopausal women. The pathophysiological mechanisms have not been elucidated but are not likely as simple as the presence or absence of estrogens, since hormone replacement therapy in elderly women in the Women's Health Initiative or the HERS Trials did not provide primary or secondary prevention against cardiovascular events. Men are also thought to be at risk for cardiovascular disease at earlier ages than women, and these mechanisms too are not likely to be as simple as the presence of testosterone since androgen levels drop in men with cardiovascular and other chronic diseases. In fact, many investigators now believe that it is the reduction in androgen levels that frequently accompanies chronic disease and may exacerbate cardiovascular disease in men. In this review the roles of sex steroids and gender in mediating or protecting against hypertension and cardiovascular disease will be discussed.

Keywords

estrogens; androgens; menopause; obesity; sympathetic nervous system; renin-angiotensin system; endothelin

The roles played by sex and gender in controlling blood pressure have not been completely elucidated, and studies have shown that these mechanisms are not as easily understood as the presence or absence of sex steroids or the sex chromosomal complement present. As discussed below, both sex steroids and chromosomes likely impact the mechanisms of blood pressure control at multiple levels.

The difference between “Sex” and “Gender”

As defined by the Institute of Medicine in its white paper, entitled “Does Sex Matter?” published in 2010 (1), “sex” differences are defined as those caused by sex organs and subsequent sex steroids, estrogens or androgens, and by sex chromosomes, XX and XY. “Gender” is a sociological term that is “a person's self representation as male or female, or

how that person is responded to by social institutions based on the individual's gender presentation. Gender is rooted in biology and shaped by environment and experience." For simplicity, unless stated otherwise, animal studies using males and females are studies into the "sex differences" in a system, since animals do not consciously self-represent as "male" or "female". In humans, unless a single sex trait is studied, e.g. prostate cancer in men or the effect of hormone replacement therapy in postmenopausal women, differences in traits in men and women connote a "gender difference".

Sex Steroids vs. Sex Chromosomes

There is a significant amount of evidence that sex steroids contribute to cardiovascular disease progression or protection, and more studies are needed to more fully determine their effects. However, in order to evaluate the role played by sex steroids versus sex chromosomes on physiological parameters, Arnold and colleagues developed the Four Core Genotype mouse models that are either Sry null or have Sry transgene expressed on an autosome providing mice that have XX females, XY males, XY females and XX males (2). When the sex steroids are manipulated by castration or ovariectomy, the contribution of sex steroids to physiology in these animals can be separated from the contribution made by sex chromosomal complement.

To date, to our knowledge, there is no information suggesting that chromosomes alone affect cardiovascular disease including hypertension. In fact, Liu and colleagues used the Four Core Genotype mouse models and reported that angiotensin converting enzyme 2 (ACE2) activity in the kidney is modulated by estradiol and the ovarian milieu, but not by testicular steroids or Y chromosome (3). However, Chen and colleagues recently exploited the four core genotype models and have shown that adiposity is due to the dosage of X chromosomes independent of the gonadal sex or Y chromosome, due to lack of X chromosome inactivation of several genes (4). Mice with 2 X chromosomes, regardless of their type of gonad, had greater adiposity and food intake during daylight hours. They also had greater weight gain on high fat diet with higher lipid and insulin levels. Blood pressure was not measured in these animals, but obesity is known to increase blood pressure (5,6). Thus the contribution of chromosomes to hypertension or cardiovascular disease independent of gonadal steroids remains to be determined.

Sex steroids and Receptors

Estrogens are the most important female sex hormones and are synthesized in the granulosa cells of the ovary in females or Sertoli cells in males. Estradiol is produced by the conversion of testosterone and androstenedione by the aromatase enzyme. There are three types of estrogen: estradiol, which is more prevalent in premenopausal women, estrone which is more prevalent during the postmenopausal period, and estriol which is increased during pregnancy primarily due to synthesis in the placenta. There are also, three estrogen receptors (ER), namely estrogen receptor alpha (ER α), estrogen receptor beta (ER β) (7,8) and the endoplasmic reticulum membrane-bound G-protein-coupled for estrogen receptor (GPER-1) a member of the G-protein-coupled receptor superfamily (9). GPER-1 is located in both intercalated cells and in tubular cells of the kidney (10), and ER β and ER α are both

present in the kidney and the vasculature (8,11,12). In the heart, ER α expression is similar in males and females, but ER β expression is higher in males (13). The age of the animals/humans studied may also be important in ER localization, since Brandenberger et al., found in the midgestational human fetus that the prevalence of ER β was greater in the kidney than ER α regardless of gender (14). In the brain, while ER α was located in nuclei of hypothalamic cells in men and premenopausal women, ER α was located in the cytoplasm in postmenopausal women (15). GPER-1 is located in highest concentrations in the hypothalamic-pituitary axis and do not bind either testosterone or progesterone (10). There is some evidence the GPER-1 may act as a mineralocorticoid receptor and bind aldosterone but this hypothesis is controversial (10). In any case, the potential differential expression and cellular and intracellular localization of the ERs and GPER-1 may explain some of the sex differences in the physiological responses to estrogens.

Testosterone is the primary male sex hormone and is synthesized in theca cells in ovaries of females and Leydig cells in testis of males. The androgen receptor (AR) has been found in most tissues. In humans two different forms of AR have been found: A and B. AR-B is predominant in all tissues in which both isoforms were detected. In fact, AR-A is not found in the kidneys of adult humans (16). In the heart, ARs are found in both males and females (13), but the subtype(s) present is not clear.

Both ERs and ARs are transcription factors that bind to estrogen or androgen response elements (EREs or AREs) upstream in the promoter regions of genes that regulate synthesis of proteins whose transcriptional and translational regulation is controlled by the steroids (7,8,16). In addition to genomic effects, sex steroids also have acute, nongenomic effects, especially in the vasculature where both estrogen and androgens cause acute vasodilation (17).

Estrogens and hypertension

Premenopausal women typically have lower blood pressure than do age-matched men (18). The National Health and Nutrition Examination Survey (NHANES) III and IV studies showed that prevalence of hypertension was greater in women, 60 years of age and older than men, regardless of ethnicity (19). The SIMONA epidemiological study (Study on Hypertension Prevalence in Menopause in the Italian population), a large cross-sectional study on 18,326 women ranging in age from 46–59 years, showed that menopause is associated with a slightly but significantly higher blood pressure, even after adjustment for age and body mass index (BMI), as well as other confounding factors. Similar results were found in other studies that demonstrated natural menopause as a risk factor for higher blood pressure, independent of age and BMI (20).

The results of the Women's Health Initiative (WHI) and Heart and Estrogen/progestin replacement study (HERS) I and II, are well known now, with hormone replacement therapy (HRT) with conjugated equine estrogen (CEE) and progestin or CEE alone failing to provide prevention against primary or secondary cardiovascular events (21–23). Moreover, these studies showed other deleterious effects of HRT, such as ischemic stroke, pulmonary emboli and other cardiovascular complications.

The effect of HRT on blood pressure is controversial. There are studies that show HRT increases blood pressure, decreases blood pressure, or has no effect (18,24–26). However, the positive or negative potential effect of estradiol on hypertension and cardiovascular disease may be age-related, since observational studies in women with premature or early menopause, estrogen is protective for ischemic stroke before age 50 years, but may become a risk factor after age 50–60 years (27).

Animal models also show age-related effects on blood pressure, some dependent on sex steroids, some not. For example, the Dahl salt sensitive rat exhibits increases in blood pressure when ovariectomized (28). In contrast, we have shown that the blood pressure in the spontaneously hypertensive rat (SHR) is independent of estrogens (29), and even in the postmenopausal period, treatment with estradiol reduces blood pressure only transiently (unpublished data, Yanes and Reckelhoff).

Androgens and hypertension

The role of androgens in mediating hypertension and cardiovascular disease is not clear. Animal studies suggest that androgens may promote cardiovascular-related diseases, including hypertension, since certain diseases are more common in men, such as myocardial infarction at an earlier age when testosterone levels are elevated. However, androgen levels are actually decreased in men with chronic diseases, including hypertension, obesity, heart disease, and chronic kidney disease (30,31). This has led many investigators to propose that the reduction in testosterone with chronic disease may somehow contribute to the disease progression and is not just a consequence of the disease (30).

Men typically have higher blood pressure and develop cardiovascular diseases earlier than women. The sexual dimorphism in blood pressure begins at puberty and persists through adult age (32–34). The prevalence of hypertension is also higher in men until after menopause in women when the prevalence of hypertension is higher in women than age-matched men (18). However, as mentioned above, androgen deficiency is associated with cardiovascular disease. For example, the Fourth Tromsø study (1994–1995), in which 1568 randomly-selected, community dwelling men were analyzed for the impact of endogenous testosterone levels on later risk for myocardial infarction and all-cause mortality. Men with free testosterone levels in the lowest quartile had a 24% greater risk for all-cause mortality due to ischemic heart disease (35). These studies did not distinguish whether the men in the lowest testosterone quartile had some undiagnosed disease process and thus had lower testosterone or whether they were healthy and yet had lower testosterone that ultimately contributed to their cardiovascular disease and death. However, in other studies total testosterone levels in older men have been shown to be inversely associated with systolic blood pressure and increased risk of death over the subsequent 20 years, independent of multiple risk factors and several preexisting health conditions (36,37).

Sex Differences in Blood Pressure

We and others have a significant amount of data showing that there are sex differences in blood pressure control in most of the major systems known to be responsible for causing hypertension. For example, we showed many years ago that while renal denervation reduced

the blood pressure in both male and female SHR, the reduction was similar in both males and females and that the blood pressure remained significantly elevated (38). These data show that the hypertension in both male and female SHR is mediated by the sympathetic nervous system, but that the sympathetics are not responsible for the sex difference in blood pressure. In addition, the fact that renal denervation failed to reduce the blood pressure to normotensive levels suggests that there are other mechanisms responsible for the hypertension in male and female SHR.

Other mechanisms include the renin-angiotensin system (RAS). We found that blockade of the RAS with enalapril, an angiotensin I converting enzyme inhibitor (ACEI), reduces blood pressure in both males and females and removes the sex difference (39). In addition, we found that treatment with ovariectomized females with testosterone increases the blood pressure in a dose dependent manner (39). In retrospect, enalapril also did not normalize the blood pressure in the SHR, as defined as blood pressure equal to 100 mm Hg, suggesting that other mechanisms contribute to the hypertension. Berecek and colleagues showed that ACE inhibitors given intracerebroventricularly reduced blood pressure to 140 mm Hg in male SHR (40), also showing that other mechanisms than central Ang II contribute to the hypertension in these rats. Since the sympathetic nervous system can stimulate the RAS and vice versa, it would be interesting to see if simultaneous blockade of both systems would normalize the blood pressure in male and female SHR.

In normotensive animals, sex differences in the pressor response to Ang II occur. Xue and colleagues reported that chronic Ang II increased blood pressure to a higher level in male rats than females (41). Sartori-Valinotti and colleagues performed similar studies in rats chronically treated with enalapril, and found that females had a greater depressor response to ACEI and had a subsequently greater pressor response to chronic Ang II infusion than did the males (42). When placed on a high salt diet, the males responded with a further increase in blood pressure whereas females did not. This is a species effect since male mice exhibited a great pressor response to chronic Ang II regardless of their treatment with chronic ACEI (43).

There are also sex differences in the role that oxidative stress plays in mediating hypertension. In male SHR, inhibiting oxidative stress with superoxide dismutase mimetics or NADPH oxidase inhibitors reduces blood pressure without having an effect on blood pressure in females (26). In addition, increasing oxidative stress with molsidomine in males increases their blood pressure (44). A competent NO system is necessary for antioxidants to reduce blood pressure since blockade of nitric oxide synthase with nitro-L-Arginine methyl ester (L-NAME) prevents antioxidants from reducing the blood pressure in male SHR (45). Whether there are gender differences in the depressor response to antioxidants has not been tested, but in general antioxidants have not been successful in clinical trials in reducing blood pressure. Perhaps the antioxidants reduced blood pressure in men but not women. In addition, if the individuals exhibited considerable endothelial dysfunction perhaps due to chronic, long term hypertension, the antioxidants may not have been able to reduce the blood pressure in the clinical trials.

There are also sex differences in the mechanisms responsible for hypertension in SHR with aging, when the blood pressure in female SHR increases to levels similar to or higher than in males (18). In males, the hypertension is mediated by the RAS since blockade with losartan, the Ang AT1 receptor antagonist, normalizes their blood pressure (46). In aging female SHR, the hypertension is mediated by endothelin (47), the RAS (46), and 20-HETE (48). The combination of losartan (AT1 receptor antagonist), Abt 627 (endothelin ET_A receptor antagonist), and 1-ABT (omega-hydroxylase inhibitor) reduced blood pressure to 110 mm Hg in these old females, but still failed to normalize the blood pressure (49). There is a contribution by the sympathetic nervous system as well since α_1 , $\beta_{1,2}$ -adrenergic receptor blockade or renal denervation reduce blood pressure but alone do not normalize it (Lima and Reckelhoff, data not published).

How Sex Steroids Could Modulate Blood Pressure

Estradiol is a vasodilator and increases nitric oxide (NO) by upregulating endothelial NO synthase (eNOS) expression chronically (50), but can also acutely increase NO due to its effect to increase intracellular calcium, a cofactor for eNOS activity. Estradiol is also modest antioxidant, although the role of oxidative stress in mediating hypertension in females has not been fully elucidated (see above) (51).

Estrogens can affect the RAS in several ways. Estrogens downregulate ACE, contributing to attenuation of synthesis of Ang II, while increasing synthesis of ACE2, the enzyme mainly responsible for synthesis of the vasodilatory peptide Ang(1-7) (52). Both effects would be anti-hypertensive. Estradiol can also downregulate the AT1 receptor (53), which would also be anti-hypertensive.

The effect of estrogens on sympathetic nervous system activity is not clear. Xue and colleagues reported a sex difference in the pressor response to aldosterone and salt with higher blood pressures developing in male rats than females, ovariectomy exacerbating, but castration having no attenuating effect on the hypertension compared to intact males (54). Interestingly, the sex difference in pressor response took 10–12 days to occur in these groups and females were protected with no significant increase in blood pressure in response to aldosterone. Central administration of estradiol blocked the hypertension in male rats given aldosterone and salt, and this protection was afforded via estrogen receptors since a non-specific estrogen receptor antagonist blocked the depressor response. Estrogen receptor antagonists given centrally also caused a pressor response to aldosterone in intact females, suggesting that the presence of estrogens protected the females from aldosterone-induced hypertension. The authors concluded that estradiol attenuated the sympathetic outflow in response to aldosterone and thus protected the animals from hypertension.

With aging, Esler and colleagues reported that sympathetic activity increases in most tissues except the kidney (55). However, the incidence of obesity increases with aging, and this is accompanied with increases in sympathetic activation (56). Thus studies are needed to fully characterize the effect of sympathetic activation on blood pressure control in pre- and post-menopausal women.

As mentioned previously, studies in animals show that androgens promote hypertension and cardiovascular disease. Studies in children by Weise and colleagues showed that norepinephrine levels increased significantly with puberty and were associated with increases in testosterone in boys, suggesting that puberty (and perhaps testosterone itself) is associated with sympathetic activation (57).

Other mechanisms by which androgens could promote hypertension include their effects to directly stimulate sodium reabsorption via the proximal tubule of the kidney, a mechanism that is blocked by AT1 receptor antagonists (58). Testosterone also increases angiotensinogen synthesis in the kidney (59,60), which could increase renin enzyme activity. Androgens have also been shown to increase endothelin levels in transsexuals taking masculinizing levels of testosterone (61).

Although testosterone supplements have become commonplace, there are few safety studies done on long term androgen treatment. However, in a short term crossover study, testosterone replacement in obese men decreased diastolic blood pressure and improved other components of metabolic syndrome (62). In male Zucker rats that are morbidly obese and have testosterone levels that are reduced by 50% compared to lean controls, testosterone supplements for 10 weeks attenuated body weight, inflammation, dyslipidemia, and insulin resistance, but unlike in the human studies, increased blood pressure (63), suggesting that additional long term studies with chronic testosterone in men with obesity are necessary since androgen supplements may be beneficial for improvement of characteristics of metabolic syndrome but their blood pressures need to be monitored carefully.

Androgen supplements in aging women and cardiovascular diseases

Androgens improve libido in women and thus are given to postmenopausal women to treat sexual dysfunction (64,65). However, there are no long term studies regarding the safety of androgen supplements, cardiovascular disease and hypertension in women. Boxer and colleagues reported data from a double-blind, randomized, placebo-controlled trial of 99 aging, frail women, that short-term therapy with dehydroepiandrosterone was safe with regard to cardiovascular risk factors (66). Nevertheless, other studies suggest that in menopause, androgen therapy could increase the risk factors for cardiovascular diseases, such as obesity, diabetes and hypertension. In a rat model of polycystic ovary syndrome produced by dihydrotestosterone (DHT) supplements, DHT caused increased food intake and body weights, increased adiposity, insulin resistance, and elevated blood pressure (67). In women there is evidence that the sympathetic nervous system is activated and may contribute to the elevated blood pressure in young women with PCOS (68), although the specific role played by androgens in the increase in sympathetic activity and the increase in blood pressure is not clear. In addition, the presence of PCOS with elevated androgens is a risk factor for increased cardiovascular disease after menopause (69). There is also evidence that androgen levels remain elevated after menopause in women who have had PCOS during their reproductive years (70). Thus the role of androgens in mediating hypertension and cardiovascular disease in aging women requires significantly more investigation.

Summary

We hypothesize that hypertension is multifactorial in both animals and humans, and that both sex chromosomes and sex steroids likely modulate the many factors that control blood. As shown in Figure 1, based on the literature, the most important factors that control blood pressure in males and females are activation of the sympathetic nervous system (SNS) and activation of the RAS to increase Ang II, the combination of which would increase sodium reabsorption by the kidney shifting pressure-natriuresis to the left and increasing blood pressure. The SNS can also activate the RAS by increasing renin release, and there is evidence, mainly in rodents, that increases in Ang II can activate the SNS. There is evidence that estrogens (54) can attenuate sympathetic activity (5) and we have unpublished data that androgens can stimulate the SNS, at least in females (Lima and Reckelhoff). Estrogens have been shown to attenuate the RAS by reducing AT1 receptor (11,53) and ACE expression (52) leading to reductions in Ang II, whereas androgens can stimulate synthesis of angiotensinogen (59,60) leading to increases in Ang II. Androgens have also been shown to increase sodium reabsorption in the proximal tubule via both androgen receptors and AT1 receptors (58). Whether estrogens affect sodium reabsorption directly is not clear. Because estrogens stimulate NO production (50), they will attenuate renal vasoconstriction both directly and by attenuating oxidative stress. Acutely androgens cause vasodilation, but whether androgens chronically cause vasoconstriction is not clear. In fact, there is evidence to suggest that the afferent arterioles of male SHR may be vasodilated compared to females since males exhibit renal injury at an earlier age than do females (71). This is supported by data from Schwartzman and colleagues showing that 20-HETE in the renal vasculature is upregulated via androgen-mediated upregulation of cytochrome P450 4A omega-hydroxylases (72). Whether estrogens can attenuate this response has not been studied. Androgens likely stimulate oxidative stress since hypertension in male, but not female, SHR and Dahl salt sensitive rats is mediated in part by oxidative stress (51). Androgens have also been shown to increase (15) and estrogens to attenuate (73) endothelin that would promote or attenuate renal vasoconstriction and sodium reabsorption, respectively.

Based on the recent studies using the four core chromosomal mice, sex chromosomes may also contribute to hypertension, whether directly or indirectly, as via X chromosomal increases in adiposity (4) that would then activate the SNS. It is also likely that sex steroids modulate the sex chromosomal effects, and that this modulation may be different in the two sexes. For example, while estrogens limit adiposity in females, androgens via their anabolic effects stimulate adiposity in females (67). Androgens decrease adiposity in males (63), and whether estrogens increase adiposity in males is not clear.

Thus more research is needed to determine how sex steroids and sex chromosomes modulate the important physiological factors that control blood pressure, and makes these exciting times for sex and gender differences studies!

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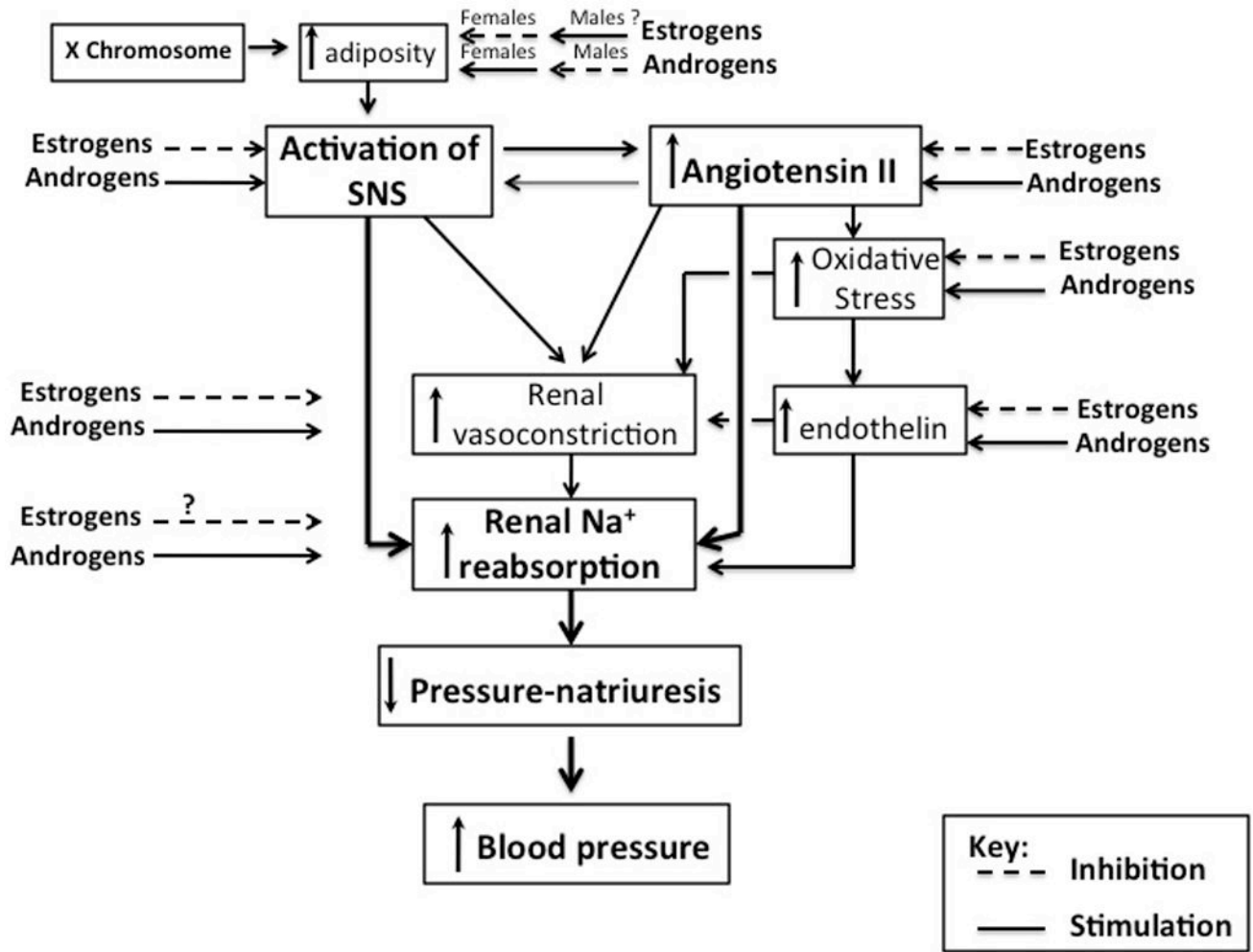


Figure 1. Potential mechanisms by which estrogens and androgens may control blood pressure.