Cardiovascular diseases are the leading cause of death in women and claim the lives of more than half a million women every year. The incidence of cardiovascular disease is 4-fold higher in postmenopausal women than in women of the same age who are premenopausal. Hypertension is a major risk factor for cardiovascular disease. It has been shown that after adjustment for age and body mass index, postmenopausal women are more than twice as likely to be hypertensive as premenopausal women. Evidence that hypertensive postmenopausal women are more salt-sensitive than normotensive postmenopausal women suggests that decreases in ovarian hormone levels and increased sensitivity to dietary sodium may be important factors in the genesis of postmenopausal hypertension. Thus, after menopause, hypertension may contribute to the increase in cardiovascular risk of postmenopausal women. The mechanisms responsible for the increase in blood pressure after menopause are still under investigation.

In the United States alone, ~38% of postmenopausal or 10 million, women use some form of hormone replacement therapy. There is quite a bit of controversy over the cardiovascular health benefits of estrogen replacement therapy, especially in light of the cessation of the estrogen-alone component of the National Heart, Lung and Blood Institute-funded Women’s Health Initiative (WHI) hormone trial earlier this year. Results of the nearly 7-year follow-up of 11,000 healthy postmenopausal women using conjugated equine estrogen or placebo who had a hysterectomy showed an increased risk of stroke and no reduction in the risk of coronary heart disease. Additionally, the estrogen plus progesterin trial of the WHI had been stopped 2 years earlier when an increased risk of breast cancer, heart disease, stroke, and blood clots were determined to outweigh the benefits of reduced risks of hip fracture and colorectal cancer in women who had a uterus. These studies have sparked a worldwide scare over the risks of hormone replacement therapy. However, potential flaws in the study should be noted in that the subjects in the WHI trial were in their 60s and early 70s and had long since gone through menopause and may have had asymptomatic cardiovascular disease (or atherosclerosis) when the study was initiated. Additionally, these clinical studies did not address a role for modulation of the renin-angiotensin system by estrogen. Therefore, there continues to be a need for continued basic research and new clinical trials on the cardiovascular effects of hormone replacement therapy.

The elegant study performed by Hinojosa-Laborde et al in this issue of Hypertension is timely, with the emphasis on the outcomes of the recent clinical trials on the benefit or lack of benefit of estrogen replacement therapy on cardiovascular risk factors in women. Hinojosa-Laborde et al determined the effects of aging and estrogen loss on the development of hypertension in Dahl salt-sensitive rats (Rapp strain) fed a phytoestrogen-free, sodium-deficient diet. The administration of a phytoestrogen-free diet is novel and points to the authors’ attempt to minimize the influence of dietary derived-estrogens on blood pressure regulation. However, pair feeding of ovariectomized (OVX) and intact rats was not performed in this study as noted by the significantly higher body weights of OVX compared with intact and OVX plus estrogen treatment at both 4 and 12 months of age (Table 1 in the Hinojosa-Laborde et al article). Therefore, the influence of elevated food/salt intake and body weights on the augmentation of blood pressure in this group of OVX rats cannot be ruled out. Requiring intensive efforts, blood pressures were measured by telemetry from 3 to 12 months of age as an extension of earlier work in which blood pressures were measured from 2 to 4 months of age in intact and OVX Dahl salt-sensitive rats on low-salt diet. In the present study, a significant increase in blood pressure was observed in intact, OVX, and OVX plus estrogen-treated rats over the 9-month period (Figure 1 in the Hinojosa-Laborde et al article). The elevation in blood pressure was quite substantial in the intact Dahl salt-sensitive rats on low-salt diet. It was not determined if the aging Dahl salt-sensitive strain exhibits a greater increase in blood pressure than the Dahl salt-resistant strain when fed a low-salt diet. However, our studies have shown that blood pressures are not elevated in the intact or OVX Dahl salt-resistant adult rat on normal-salt diet. The effect of low-salt or normal-salt diet to enhance blood pressure in Dahl salt-sensitive rats after OVX is in agreement with previous studies. In the current study, mean arterial blood pressure was highest in the OVX and lowest in the OVX plus estrogen-treated rats. Estrogen replacement therapy in OVX rats reduced mean blood pressure by 25 mm Hg compared with OVX alone. It is worth noting that a similar degree of lowering of systolic blood pressure (35 mm Hg) by estrogen in OVX Dahl salt-sensitive rats (Brookhaven strain) pair-fed to intact rats in which blood pressures were measured by...
conscious tail-cuff methodology has been reported,\textsuperscript{12} indicating that the 2 methodologies provide data that result in a similar conclusion.

The data by Hinojosa-LaBorde et al\textsuperscript{10} show a positive correlation between increases in blood pressure and AT\textsubscript{1} receptor binding in both the adrenal cortex and glomeruli of estrogen-depleted animals and an attenuation of both of these effects by estrogen replacement therapy. Evidence for upregulation of the AT\textsubscript{1} receptor and presumably an overactivation of the renin-angiotensin system in these 2 important target organs for angiotensin II effects on sodium homeostasis point to a loss of estrogen modulation of the renin-angiotensin system, which may play a role in postmenopausal hypertension. This work confirms our recent study that showed an effect of estrogen to reverse the elevated AT\textsubscript{1} receptor protein expression in the kidney of Dahl salt-sensitive rats after OVX.\textsuperscript{12} In addition, we have demonstrated that chronic blockade of the AT\textsubscript{1} receptor normalized blood pressure in OVX Dahl salt-sensitive rats, indicating that the AT\textsubscript{1} receptor does have a role in the hypertension process and may be involved in the increased salt sensitivity.\textsuperscript{12} Therefore, together these studies support a role for modulation of the renin-angiotensin system by estrogen and may provide an additional target for reducing the risks of cardiovascular disease in postmenopausal women.

Therefore, we are just beginning to understand the pathophysiology of postmenopausal hypertension. After menopause, loss of the vascular-protective effects of estrogens may unmask a population of women prone to hypertension who are at higher risk for cardiovascular morbidity. Our studies\textsuperscript{12} and those by Hinojosa-LaBorde\textsuperscript{10,11} suggest that salt-sensitive premenopausal women may be protected against the development of hypertension because of the presence of ovarian hormones and that after menopause or ovariectomy, the protective effects of these hormones are lost, thus contributing to the development of hypertension. Particularly in light of the disappointing cardioprotective results obtained in several clinical trials with hormone replacement therapy, the mechanisms underlying the estrogen and renin-angiotensin system interaction merit further study. It is anticipated that new results obtained from basic research and clinical trials will provide insight into the mechanisms of cardiovascular injury that are clinically relevant and may provide the basis for new therapies.

\textbf{References}

Targeting of the Renin-Angiotensin System as an Adjunct to Estrogen Replacement Therapy
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