Editorial Commentary

Hypertension and Antihypertensive Therapy in Elderly Women
How Much Do We Really Know?

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Hypertension is a major public health problem worldwide, affecting more than 50 million Americans. It is a major risk factor for target organ damage resulting in coronary artery disease, heart failure, stroke, and kidney disease. Large epidemiological surveys have shown that more women, primarily elderly women, than men have hypertension.[1] Therefore, in addition to age[2] and race,[3] gender seems to influence significantly the natural history of hypertension and probably the selection of antihypertensive agents and the response to treatment.

Gender and age differences in blood pressure have been suggested to be associated with the sex hormones. Among these, estrogen is proposed to be responsible for the lower blood pressure in premenopausal young women. The cardioprotective effects of estrogen, though controversial in postmenopausal women,[4,5] have been suggested by multiple studies in experimental animals and in humans, and the loss of endogenous estrogen with aging contributes to the rapid increase in the incidence of coronary artery disease after menopause. Estrogen improves lipoprotein profiles, has vasodilatory effects on the endothelium, and inhibits vascular smooth muscle cell growth and constriction. However, the time course of the maximal decrease in blood pressure does not coincide with the maximal rise in hormone levels, suggesting that the relationship between blood pressure and endogenous levels of hormones is complex and is probably affected by other factors.[6]

Alternatively, it was found that menopause was accompanied by a steeper rise of systolic pressure with age and by an increase in the absolute level of diastolic pressure, which was independent of age.[7] One recent study demonstrated that aging was accompanied by a greater increase in sympathetic traffic in women than in men, independent of menopausal status.[8] These results parallel epidemiological data indicating a higher prevalence of hypertension in elderly women and suggest that sympathetic neural mechanisms may contribute importantly to the more marked influence of aging on blood pressure and cardiovascular disease in women. Additionally, these results are consistent with the findings of Matsukawa et al[9] in Japanese subjects. Thus, enhanced age-related sympathetic activation in women is not race-specific.

Laitinen et al[10] investigated age dependency of cardiovascular autonomic responses to head-up tilt in healthy human individuals and found that the increase in heart rate was more pronounced in the young subjects, whereas the increase in peripheral resistance was predominantly observed in the elderly during upright tilt. These data suggest that vascular responses related to vasoactive mechanisms and vascular sympathetic regulation become augmented with increasing age. Although the study by Laitinen et al[10] focused on age but not gender, it seems likely that augmented sympathetic vasoconstriction plays a more critical role in elderly hypertensive women. Indeed, this notion was supported by the recent findings of Lipsitz et al.[11]

In this edition of *Hypertension*, Lipsitz et al[11] provided evidence of enhanced vasoreactivity in hypertensive elderly women. In this study, the authors carefully examined the physiological responses to a graded upright tilt in healthy normotensive, controlled hypertensive, and uncontrolled hypertensive elderly men and women. They found that in contrast to other groups, elderly hypertensive women had a tendency toward an orthostatic increase in blood pressure during graded upright tilt, which was associated with a significant increase in systemic vascular resistance (SVR). This increase in blood pressure and SVR was not seen in hypertensive men. Furthermore, this response was associated with greater low-frequency systolic blood pressure variability, a presumed marker of sympathetic control of the vasculature. Interestingly, forearm vascular resistance remained unchanged during tilt, despite an increase in SVR. The possible underlying mechanisms proposed by the authors included gender-related differences in vascular baroreflex gain, enhanced sensitivity to circulating vasoconstrictors, and/or reduced sensitivity to vasodilators. The similar forearm vascular resistance in hypertensive women and men suggested that increases in resistance took place in other vascular beds (eg, splanchnic, skin, etc.). However, this differential response in directly measured regional vascular beds (forearm muscle) and indirectly estimated SVR does suggest some caution be used in interpreting the results. For example, SVR was estimated from mean blood pressure (derived from finger blood pressure) and cardiac output derived from thoracic impedance. It is possible that there are systematic errors associated with both of these measurements that are most prominent in elderly women with systolic hypertension. Thus either overestimation of mean blood pressure from finger blood pressure during tilt induced vasoconstriction or underestimation of cardiac output due to changes in the myriad of factors that go into the impedance calculation (aortic and pulmonary compliance, thoracic fluid content, body composition, lung volume, hematocrit, length of the blood column, etc.) may change differently during tilting.

The graded upright tilt test was repeated after 6 months of observation (for controls) or pharmacological therapy for

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(*Hypertension*. 2006;47:323-324.)

***Hypertension* is available at http://www.hypertensionaha.org**
DOI: 10.1161/01.HYP.0000202597.91523.7e

uncontrolled hypertensive subjects. They found that after successful antihypertensive therapy, blood pressure fell to normal ranges in both men and women and remained stable during upright tilt. This improvement in blood pressure regulation was associated with attenuation of the SVR response, improved carotid distensibility, and a reduction in low-frequency systolic blood pressure variability. The authors considered that these observations could probably be attributed to a reduction in sympathetic tone or arterial remodeling after antihypertensive therapy in elderly hypertensive women.

What are the clinical implications of these findings? As the authors state in the article, a heightened vascular response to sympathetic activation during orthostasis may contribute to the excessive cardiovascular morbidity and mortality that has been observed in elderly hypertensive women. The additional afterload placed on the left ventricle may contribute to cardiac ischemia, left ventricular hypertrophy, and ultimately cardiac decompensation. Their results highlight the beneficial effects of antihypertensive therapy on the systemic vasculature, particularly for elderly women in whom enhanced vasoreactivity may contribute to excessive cardiovascular morbidity and mortality.

Since sympathetic nerve activity was not measured in this study, it is difficult to determine whether the attenuated SVR response was due to a reduction in sympathetic activation. We previously found that chronic antihypertensive therapy (combined losartan and hydrochlorothiazide) caused sustained reductions in arterial pressure and total peripheral resistance in middle-aged male patients with moderate essential hypertension; however, there was a marked and persistent increase in muscle sympathetic nerve activity (MSNA) after treatment.[12] In the study by Lipsitz et al[11] uncontrolled hypertensive subjects were treated with either lisinopril alone or in combination with hydrochlorothiazide and/or amplodine, and if lisinopril was not tolerated, an angiotension receptor blocker was used. It would have been instructive to know what the distribution of this differential therapy was among the patients in this study (ie, how many patients were treated with single, double, or triple therapy). Results regarding the effects of these antihypertensive drugs on MSNA in patients with hypertension are controversial. There is no information available on whether different antihypertensive regimens can affect MSNA responses differently in elderly hypertensive men and women. Until direct measurements of sympathetic activity can be made under conditions similar to this study, interpretation from indirect measures of sympathetic activation derived from changes in cardiovascular variability should be considered preliminary and hypothesis-generating. Moreover, other interpretations of the data are possible. For example, because no acute measurements were made following initiation of antihypertensive therapy, it cannot be determined from this design whether the observations made by the authors are due to long standing antihypertensive therapy or rather to the acute effects of vasodilation.

Investigations of gender differences in pathophysiology and response to treatment of essential hypertension have not been extensive. The findings of Lipsitz et al[11] provide some important insights into the mechanisms underlying the high prevalence of hypertension in elderly women. The direct comparison of men and women of the same age and the same mean blood pressure has never been studied prospectively in a large population for the reduction of cardiovascular risk. Therefore, whether the drug treatment of hypertension in women, particularly in elderly women, is identical or different from that in men remains to be clearly identified. Women, until recently, have been under-represented in clinical trials, raising concerns as to the applicability of current guidelines for the diagnosis and treatment of hypertensive cardiovascular disease.[13] The study by Lipsitz et al suggests that angiotensin-converting enzyme inhibitors plus dihydropyridine calcium channel blockers may be a particularly effective combination in elderly women with systolic hypertension. This hypothesis could be tested in studies that are already completed[14] or in prospectively designed trials. Finally, it should be noted that the difference among groups was most marked in the upright, tilted position. This observation raises the possibility that changes in *ambulatory* blood pressure induced by this drug combination in elderly women may be even more marked than blood pressure measured in the routine clinic setting using guidelines of the seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

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