Neural and Nonneural Mechanisms for Sex Differences in Elderly Hypertension
Can Exercise Training Help?

Qi Fu, Wanpen Vongpatanasin, Benjamin D. Levine

Blood pressure (BP) increases with advancing age in humans in most industrialized societies. The relationship between systolic and diastolic pressures to cardiovascular events is generally more pronounced in people aged ≥65 years. The Framingham Heart Study and the National Health and Nutrition Examination Survey uniformly demonstrated a higher prevalence of hypertension and a lower BP control rate in elderly women than in men. Specifically, only 23% to 28% of hypertensive women over the age of 60 years achieved BP goals on treatment, whereas 36% to 38% of hypertensive men of the same age reached the target BP. Precise mechanisms for this observation are unknown but may be related to sex differences in the pathophysiology of hypertension or responses to antihypertensive therapy.

It has been recognized that the pathophysiology of hypertension in the elderly is largely attributed to an age-related decline in aortic distensibility resulting in progressive increases in systolic pressure and pulse pressure and a decrease in diastolic pressure. However, large epidemiological studies have shown that not only systolic but also diastolic pressure is higher in elderly women than in men, suggesting that other mechanism(s) may contribute to sex differences in BP regulation. For example, one recent study demonstrated that aging was accompanied by a greater increase in sympathetic traffic in healthy women than in men. It is well known that elevated sympathetic activity plays an important role in the development of hypertension in the young and middle-aged population. Whether a sympathetic neural mechanism is responsible for the high prevalence of hypertension and the poor BP control rate in elderly women remains unclear. In addition, whether ventricular-arterial function and some hormonal markers are nonneural differences that may also contribute to the influence of aging on BP control in elderly women needs to be verified.

Clarifying the specific pathophysiology of sex differences in elderly hypertension is essential for determining optimal evidence-based therapy, particularly because the risk of stroke, myocardial infarction, or congestive heart failure remains high in these patients even with adequate BP control; moreover, many patients have inadequate BP control despite medical therapy, often involving multiple drug regimens. A potential mechanism for both of these problems could be persistent or even augmented sympathetic activation by the baroreflex during antihypertensive drug therapy. One complementary nonpharmacologic therapy that may have some promise to reduce sympathetic activation and/or arterial stiffening with limited adverse effects is exercise training. However, it is unknown whether exercise training can be regarded as an effective therapy for elderly hypertensive patients compared with standard pharmacological therapies.

In this review, we highlighted some previous results of neural and nonneural control in elderly hypertensive subjects, as well as exercise training as a nondrug antihypertensive therapy in this particularly challenging patient population. An overview of neural and nonneural mechanisms and the possible role of exercise training is depicted in Figure 1. The techniques used in previous studies to assess neural and nonneural control in hypertensive patients are summarized in Table 1.

Aging, Sex, and Neural Control in Hypertension

Sympathetic neural control plays an important role in arterial pressure maintenance in humans. Vasomotor sympathetic activity, which can be recorded as muscle sympathetic nerve activity by the microneurographic technique, has been found to increase with advancing age, whereas the increment is greater in women than in men (Figure 2). One recent study demonstrated that the increase in BP per increment of muscle sympathetic nerve activity was actually greater in women over the age of 40 years than in similarly aged men. These results parallel epidemiological data indicating a higher prevalence of hypertension in elderly women and suggest that a sympathetic neural mechanism may contribute importantly to the more marked influence of aging on BP and cardiovascular disease in women.

Laitinen et al showed that, during upright posture, the increase in heart rate was more pronounced in young indi-
individuals, whereas the increase in peripheral vascular resistance was more dramatic in the elderly, suggesting that vascular responses related to vasoactive mechanisms and vasomotor sympathetic regulation become augmented with increasing age. Although the study by Laitinen et al19 focused on age but not sex, it seems likely that augmented sympathetic vasoconstriction plays a more critical role in elderly hypertensive women. Indeed, this notion was supported by the findings of Lipsitz et al,20 showing enhanced vasoreactivity in elderly hypertensive women. They found that elderly hypertensive women had a much greater increase in systemic vascular resistance than elderly hypertensive men during upright tilt, which was associated with a greater low-frequency systolic pressure variability, a presumed marker of sympathetic vaso-

Table 1. Techniques Used to Assess Neural and Nonneural Controls in Hypertensive Patients

<table>
<thead>
<tr>
<th>Mechanisms</th>
<th>Techniques</th>
<th>Measurements</th>
<th>Authors, Year, Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neural</td>
<td>High-performance liquid chromatography</td>
<td>Plasma catecholamines</td>
<td>Goldstein, 19837</td>
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<td>Goldstein, 19818</td>
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<td>Goldstein et al, 19839</td>
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<td></td>
<td>Fu et al, 200513</td>
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<td></td>
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<td></td>
<td>Laitinen et al, 199826</td>
</tr>
<tr>
<td></td>
<td>The radiotracer technique</td>
<td>Norepinephrine spillover</td>
<td>Esler et al, 198099</td>
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<td></td>
<td></td>
<td>Extravascular norepinephrine release rate</td>
<td>Brown et al, 200271</td>
</tr>
<tr>
<td></td>
<td>The microneurographic technique</td>
<td>Muscle sympathetic nerve activity</td>
<td>Fu et al, 200513</td>
</tr>
<tr>
<td></td>
<td>Spectral and transfer function analysis</td>
<td>Baroreflex gain</td>
<td>Lipsitz et al, 200520</td>
</tr>
<tr>
<td></td>
<td>The modified Oxford method</td>
<td>Baroreflex gain</td>
<td>Sevre et al, 200127</td>
</tr>
<tr>
<td></td>
<td>Nonneural</td>
<td>Arterial stiffness/compliance</td>
<td>van Popele et al, 200128</td>
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<td></td>
<td>Doppler ultrasound technique</td>
<td></td>
<td>Boutouyrie et al, 200229</td>
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<td></td>
<td>Tonometry</td>
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<td>Waddell et al, 200138</td>
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<tr>
<td></td>
<td>Echocardiography</td>
<td></td>
<td>Berry et al, 200440</td>
</tr>
<tr>
<td></td>
<td>Acetylene rebreathing technique</td>
<td></td>
<td>Ferrier et al, 200159</td>
</tr>
<tr>
<td></td>
<td>MRI</td>
<td></td>
<td>Rinder et al, 200441</td>
</tr>
<tr>
<td></td>
<td>Left ventricular size and geometry and function</td>
<td>Arterial afterload</td>
<td>Fu et al, 200513</td>
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<td></td>
<td></td>
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<td>Burns et al, 200773</td>
</tr>
</tbody>
</table>
It was shown that a decrease in sympathetic activity occurred in response to increased vascular resistance in these patients. It was proposed that the enhanced vascular resistance response was not measured in this study, it is difficult to be certain whether the enhanced vascular resistance response was because of an increase in sympathetic outflow in these patients. It was shown that α-adrenergic vasoconstriction was blunted despite elevated sympathetic activity in the peripheral and renal arteries in healthy elderly men. Mechanisms underlying this observation are unknown, but a recent study in rats indicates that aging is associated with a decline in α-adrenergic receptor expression and binding affinity in male rats but not in female rats. Therefore, a sex-specific, age-related difference in α-adrenergic vasoconstriction may also contribute to the enhanced vasoreactivity in elderly hypertensive women.

Previous studies have suggested that hypertension is associated with a resetting of the cardiovascular baroreflex arc at a higher set point. With the spectral transfer function analysis technique, it was found that the sensitivity of baroreflex control of the heart rate did not differ between normotensive men and women, but hypertensive patients had lower baroreflex sensitivity than normotensive control subjects; moreover, cardiovascular baroreflex sensitivity was significantly reduced in middle-aged hypertensive women compared with age-matched hypertensive men. It was proposed that sex was an important determinant of the cardiovascular baroreflex sensitivity and heart rate variability in hypertensive individuals. Conversely, although there is nearly universal agreement that human hypertension is associated with impairment of baroreflex control of cardiac vagal outflow, it is still not completely certain whether human hypertension is associated with a corresponding enhancement of sympathetic outflow; whether baroreflex control of vasomotor sympathetic activity is impaired in hypertensive subjects, especially in hypertensive seniors; and whether the impairment of sympathetic baroreflex function is age and sex dependent in hypertensive patients.

**Nonneural Mechanism for Sex Differences in Elderly Hypertension**

Increased ventricular-arterial stiffness is associated with hypertension and is recognized as an important determinant of cardiovascular risk. It was found recently that advancing age and female sex were associated with increases in vascular and ventricular stiffness even in the absence of cardiovascular disease. An increased prevalence of isolated systolic hypertension in elderly women has been proposed to be associated with an increase in arterial stiffness. One hemodynamic consequence of vascular stiffening is an increase in left ventricular afterload. However, there is strong evidence that vascular resistance is not the dominant factor in the rise in systolic pressure after the age of 60 years. For example, it was found that total peripheral resistance was only marginally elevated in elderly patients with isolated systolic hypertension compared with age- and sex-matched normotensive control subjects. On the other hand, it was shown that an augmentation of aortic pressure throughout systole (large artery stiffness and early pulse wave reflection) predominated over increased vascular resistance in these elderly patients.

Age and hypertension are associated with alterations in the elastic properties of the arterial wall that cause profound changes in arterial pressure waves, whereas these changes are attributed primarily to the changes in amplitude and timing of pulse wave reflections from peripheral reflecting sites in the lower body. There is increasing evidence to support the concept that the age-related increase in aortic stiffness is significantly greater in women than in men (Figure 3). A recent study by Berry et al. found that elderly systolic hypertensive women had stiffer large arteries, greater central wave reflection, and higher pulse pressure than elderly hypertensive men, and they thereby concluded that stiffer large arteries likely contributed to the greater prevalence of systolic hypertension in elderly women and may partly explain the acceleration in postmenopausal cerebrovascular and cardiac complications. However, the Third National Health and Nutrition Examination Survey showed that not only systolic but also diastolic pressure was higher in elderly women compared with elderly men. Whether the greater prevalence of diastolic hypertension and/or combined systolic-diastolic hypertension in elderly women can also be explained by impaired ventricular-arterial function alone or whether other mechanisms play an additional role remains unclear.

It has been shown that menopause is associated with increased susceptibility to a salt-induced rise in BP. Schulman et al. demonstrated that salt sensitivity of BP increased significantly 4 months after surgical menopause in middle-aged women, which could be related to increased angiotensin receptor subtype 1 expression in the kidney. Salt-sensitive hypertensive patients have a higher incidence of left ventricular hypertrophy, endothelial dysfunction, insulin resistance, and hyperlipidemia compared with salt-resistant hypertensive patients. Thus, decreases in sex hormones and increased sensitivity to sodium may be important factors in the genesis of postmenopausal hypertension.

**Effects of Exercise Training on Neural and Nonneural Control in Elderly Hypertension**

Aging generally leads to reductions in physical activity in both humans and animals. A sedentary lifestyle increases the risk of hypertension, whereas increased physical activity or...
exercise training is associated with lower levels of BP.\textsuperscript{52,53} We found that a sedentary lifestyle during normal aging led to cardiac atrophy and an increase in arterial elastance/stiffness, whereas very prolonged exercise training prevented ventricular-arterial stiffening (Figure 4).\textsuperscript{54} Recently, we demonstrated that 3 to 6 months of endurance training in initially sedentary seniors reduced both systolic and diastolic pressures effectively.\textsuperscript{55} Training-induced reduction in BP has been proposed to be associated with an increased release of NO, resulting from an increase in vascular shear stress during exercise.\textsuperscript{56} Chronic increases in shear stresses lead to function and histological alterations of vascular endothelium, causing enhanced vascular structure and function.\textsuperscript{57}

Exercise training was found to improve arterial compliance in healthy middle-aged individuals,\textsuperscript{58} but it was reported that short-term (ie, 8 weeks) training did not modify large-artery compliance and left ventricular mass or function in elderly patients with isolated systolic hypertension.\textsuperscript{59} However, one recent study showed that, although arterial compliance remained unchanged, flow-mediated endothelium-dependent vasodilation increased after 12 weeks of training in elderly hypertensive subjects, indicating improved endothelial function.\textsuperscript{60} Rinder et al\textsuperscript{61} found that long-term (ie, 6 months) training not only decreased BP but also induced regression of left ventricular hypertrophy in elderly hypertensive patients. Recently, Westhoff et al\textsuperscript{62} demonstrated in elderly hypertensive subjects that 12 weeks of training evoked comparable reductions in BP and improvements of endothelial function in the presence and absence of β-blockades, suggesting that drug therapy provided no additive benefit to and did not prevent the antihypertensive effects of exercise training. These results are consistent with some previous reports with both selective and nonselective β-blockade, as well as calcium channel blockers.\textsuperscript{63–68}
Grassi et al showed in young hypertensive men that the BP reduction after training was mediated by a neural mechanism, because vasomotor sympathetic activity decreased after 10 weeks of training. Similar results were obtained in middle-aged and elderly hypertensive subjects after 4 and 6 months of training, indicating that suppression of sympathetic activity may play a role in the reduction in arterial pressure. In addition, the sympathetic baroreflex function was improved after training in middle-aged hypertensive patients. Elevated sympathetic activity was found to be associated with an increase in arterial wall thickening and left ventricular mass. Thus, training-induced decreases in sympathetic activity may be beneficial in preventing arterial stiffening in hypertension.

Exercise training could elicit adaptations in the adrenergic system, because the sympathetic nervous system is activated during each bout of exercise, and repeated activation of the sympathetic nervous system may result in an attenuation of sympathetic activity. Animal studies suggested that NO decreased overall sympathetic excitability within the brain stem and possibly through actions in higher brain regions (ie, hypothalamus). Because of the inevitable experimental restrictions, it is unclear whether the increased release of NO during exercise training has a central sympathoinhibitory effect in humans. It is also unclear whether training reduces salt sensitivity in elderly women. Previous studies demonstrated that hyperinsulinemia and insulin resistance were associated with hypertension and sympathetic activation, whereas training could improve insulin sensitivity in normotensive and hypertensive individuals. Training-induced muscle adaptations also appear to be important in attenuating insulin-mediated sympathetic activation. In addition, exercise training has been shown to improve aerobic capacity and vascular conductance and to lower body fat, each of which

Table 2. Effects of Endurance Exercise Training on Neural and Nonneural Mechanisms in Hypertensive Patients

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Authors, Year, Reference</th>
<th>Patient Characteristics</th>
<th>Measured Variables</th>
<th>Training Program</th>
<th>Training Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neural</td>
<td>Brown et al, 200221</td>
<td>Mild hypertensive subjects (18 women, 12 men, mean age 63 y)</td>
<td>NE2 (an index of SNA)</td>
<td>Walking/jogging/cycling at 70% of HRpeak, 3 times/wk, 40 min per time for 6 mo</td>
<td>No change in BP</td>
</tr>
<tr>
<td></td>
<td>Laterza et al, 200770</td>
<td>Mild hypertensive subjects (7 women, 7 men, mean age 44 y)</td>
<td>MSNA, Sympathetic baroreflex function</td>
<td>Cycling at 70% of VO2peak, plus strength training, 60 min per time, 3 times per wk for 4 mo</td>
<td>Decreased BP</td>
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<td></td>
<td>Kouame et al, 199552</td>
<td>Mild-to-moderate hypertensive subjects (1 woman, 8 men, mean age 43 y)</td>
<td>Baroreflex control of limb vascular resistance</td>
<td>Cycling at 50% and 70% of VO2peak, 3 times per wk, 45 min per time for 10 wk each</td>
<td>Restored baroreflex function</td>
</tr>
<tr>
<td>Nonneural</td>
<td>Ferrier et al, 200119</td>
<td>Mild isolated systolic hypertensive subjects (5 women, 5 men, mean age 64 y)</td>
<td>Large-artery compliance</td>
<td>Cycling at 65% of HRpeak, 3 times per wk, 40 min per time for 8 wk</td>
<td>No change in BP</td>
</tr>
<tr>
<td></td>
<td>Rinder et al, 200441</td>
<td>Mild-to-moderate hypertensive subjects (3 women, 13 men, mean age 66 y)</td>
<td>Left ventricular mass or function</td>
<td>Walking/jogging/cycling at 60–70% of HRpeak, ≥3 times per wk, 40 to 50 min per time for 6 mo</td>
<td>Decreased BP</td>
</tr>
<tr>
<td></td>
<td>Westhoff et al, 200762</td>
<td>Mild-to-moderate hypertensive subjects (13 women, 12 men, mean age 68 y)</td>
<td>Endothelial function assessed by flow-mediated dilation</td>
<td>Interval training (treadmill walking, with or without β-blockades), 30 to 40 min per time, 3 times per wk for 12 wk</td>
<td>Improved endothelial function in all patients</td>
</tr>
<tr>
<td></td>
<td>Higashi et al, 199993</td>
<td>Mild hypertensive subjects (4 women, 13 men, mean age 47 y)</td>
<td>Endothelium-dependent forearm vasorelaxation</td>
<td>Brisk walking at 50% to 60% of VO2peak, 30 min per time, 5 to 7 times per wk for 12 wk</td>
<td>Decreased BP</td>
</tr>
<tr>
<td></td>
<td>Turner et al, 200045</td>
<td>Mild-to-moderate hypertensive subjects (2 women, 9 men, mean age 65 y)</td>
<td>Left ventricular size and geometry and function</td>
<td>Walking/jogging/cycling at 60% to 80% of HRpeak, 30 to 50 min per time, 4 times per wk for 7 mo</td>
<td>Partial regression of left ventricle</td>
</tr>
</tbody>
</table>

NE2 indicates extravascular norepinephrine release rate; SNA, sympathetic nerve activity; MSNA, muscle sympathetic nerve activity; VO2peak and HRpeak, peak oxygen uptake and peak heart rate during maximal exercise test.
could also contribute to a reduction in BP.81–85 The improved vascular conductance in athletes and with training is not endothelial mediated and probably reflects structural adaptations required to accommodate a high muscle blood flow.84,85

Sex differences in training-induced BP reduction in elderly hypertensive subjects have not been investigated extensively. It was found in a Japanese population that elderly hypertensive subjects experienced smaller reductions in BP than younger counterparts after 8 weeks of training, whereas sex did not affect the efficacy of physical activity for lowering elevated BP.86 Brown et al71 showed similar results, but sex was not investigated in their study. These observations cannot be explained by a suboptimal training stimulus, because maximal oxygen uptake increased similarly (ie, 14% to 16%) in young and elderly patients after training in both studies. Rather, persistent sympathetic activation and ventricular-arterial stiffening may be potential mechanisms underlying the attenuated training-induced BP reduction in hypertensive seniors. Unfortunately, comparisons of training effects on neural and nonneural control in elderly hypertensive men and women have never been made in the same study, although 2 previous investigations have looked extensively at the effects of training in hypertensive women87,88 without direct measurements of muscle sympathetic nerve activity. Whether exercise training can be regarded as an effective therapy for elderly hypertensive patients needs to be clarified. Table 2 shows the effects of training on neural and nonneural control of BP in hypertensive patients from previous studies.

Significance

It is important to note that approximately two thirds of elderly hypertensive women, who are most at risk for stroke and cardiovascular events, do not have their BP adequately controlled, either because they are not on drug treatment or because, in spite of taking antihypertensive drugs, their BP is still above recommended levels. The questions of which drug classes offer the most benefit for these patients; whether antihypertensive drug treatment should be the same or different for elderly men and women; and whether nonpharmacologic therapy, such as exercise training, is effective for elderly hypertensive women are as yet unanswered. If a heightened level of sympathetic activity coupled with elevated arterial stiffness is the fundamental mechanism of hypertension in elderly women, which cannot be reversed by most antihypertensive agents, exercise training may be an integral strategy to achieve BP control in this patient population by reducing both sympathoexcitation and arterial stiffness. If this is the case, formal exercise training should be incorporated as an essential part of hypertension treatment in elderly hypertensive women in addition to BP medications.

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Disclosures

None.

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53. Fu et al Aging, Sex, Hypertension, and Role of Exercise 793


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