Women Are Not Just Small Men! Sex Differences in Blood Pressure Control

By Jane F. Reckelhoff

Hypertension is a common condition that is a significant risk factor for development of other cardiovascular diseases. The prevalence of hypertension is higher in men than women until after menopause, when the prevalence reverses and is higher in women. In addition, more women die of cardiovascular disease each year than do men.

There is mounting evidence that blood pressure in women is less well controlled than in age-matched men, despite the facts that women see their physicians more frequently and are often more compliant with their medications than men. This statistic makes one consider that either physicians are not as aggressive in treating hypertension in women, which is possibility, or that what causes hypertension in women may not be the same as what causes hypertension in men. Yet the guidelines for treatment for hypertension are the same for men and women based on data mostly collected in men, or if women were included in the studies, there were no analyses of the data to separate responses to antihypertensive therapy in men and women.

This leads to the notion in hypertension treatment that "women are just small men"—we treat their hypertension the same, even the doses of drugs are the same despite significant body weight differences between men and women that may suggest that kinetics and utilization of drugs may also be different.

The reason I think this is important is based on our animal experiments. We have studied aged male and female spontaneously hypertensive rats and found that the blood pressure in old males can be well controlled to normotensive levels by angiotensin receptor blockers (ARBs) or angiotensin I converting enzyme (ACE) inhibitors, suggesting that the renin-angiotensin system is the major system that affects blood pressure in the males.

In the old females, however, ARBs or ACE inhibitors reduce blood pressure but don't normalize it. Also, endothelin ETA receptor antagonists reduce blood pressure but don't normalize it. 20-hydroxyeicosatetraeonic acid (20-HETE) synthesis inhibitors reduce blood pressure but don't normalize it. The combination of ARBs, endothelin ETA receptor antagonists, and 20-HETE inhibitors given together significantly reduce blood pressure in the old females, but still doesn't normalize it (their blood pressure remains at 110 mm Hg mean blood pressure, measured by 24-hour telemetry, where the definition of "normal" is 100 mm Hg). These old females are no longer estrous cycling, which is similar to menopause in women. Also, bear in mind that these rats are inbred and raised in barriers, and so have little genetic variation or environmental confounding effects compared to humans. Based on these data, it's not surprising that blood pressure control in women, especially postmenopausal women, confounded by genetics and environmental conditions may be difficult to manage! It also surprising that very few human studies have been done in which gender differences in responses to antihypertensive therapies have even been evaluated!

So what can we do as clinicians and scientists? First of all, make the NIH put teeth into their rules for human subject studies and require that all studies be powered to evaluate gender-specific differences. This is as important for men as for women, and the finding that there is no gender difference in responses is as important as finding them. The second thing is to advocate that women are not just "little men," with different genetics and environmental conditions that may differentially affect their incidence of diseases, disease progression, treatment, and responses to that treatment. Finally, as new drug therapies for hypertension, or any other disease for that matter, come on the market we should advocate for gender differences studies in responses to make certain we are treating women and men with the best available therapies for their "differences" or "similarities."

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The Role of Renal Denervation in the Management of Hypertension

By Laura P. Svetkey and Crystal C. Tyson

Renal denervation is an emerging and promising new therapy for resistant hypertension. Although 54 percent of all hypertension is "uncontrolled" (1), not all uncontrolled hypertension is considered resistant. The American Heart Association (AHA) definition of resistant hypertension is BP above goal on at least three antihypertensive medications of different classes, one of which is a diuretic, or BP that requires four or more medications to get to goal. Prevalence in the general hypertensive population is relatively low, but resistant hypertension is commonly seen in nephrology offices.

In evaluating a patient with resistant hypertension, it's important to consider reversible underlying causes, titrate current medications to maximum tolerated dose, and optimize adherence to both pharmacologic and lifestyle treatments. Thereafter, management involves the addition of one more medication after another. If each subsequent addition significantly lowers BP, even if it never gets to goal, then this treatment strategy is advantageous. However, taking four or more medications involves both financial and potential side effect burdens. A potential new treatment for resistant hypertension is on the horizon: renal denervation.

Renal denervation, achieved by radiofrequency ablation through an intra-arterial catheter, directly addresses the extent to which resistant hypertension is due to sympathetic overactivity. Denervation reduces efferent nerve activity (i.e., from the central nervous system [CNS] to the kidney) thus lowering renin secretion, stimulating natriuresis, and improving renal hemodynamics. It also reduces renal afferent nerve activity (i.e., from the kidney to the CNS) thus reducing outflow to the CNS and contralateral kidney, which further dampens sympathetic activity.

Human trials conducted outside the United States are very promising: in one randomized, controlled trial of 106 hypertensive patients, net reduction in BP 6 months after denervation was 33/11 mm Hg compared to control (2). Blood pressure reduction persisted for 12 months. There was no excess risk of renal damage or hypotension.

Larger trials in the United States, involving at least three different ablation devices, are either ongoing or planned for the near future. If these trials replicate the non–U.S. trials, it is reasonable to expect U.S. Food and Drug Administration (FDA) approval within the next year or two.

In considering implementation of this new treatment modality, there are several questions to consider:

Is renal denervation effective and safe in patients with chronic kidney disease (CKD)? The failing, ischemic kidney contributes to sympathetic hyperactivity, suggesting that patients with CKD may have greater BP lowering from denervation than those with normal kidney function. Pilot data in small numbers of patients with stage 3 to 4 CKD (3) and in ESRD (4,5) suggest favorable results, but in ESRD small renal arteries may limit feasibility. Results are promising in CKD, but clearly additional research is needed.

Is renal denervation a reasonable treatment option in patients with less severe hypertension? Most trials to date have enrolled patients with AHA-defined resistant hypertension and systolic BP greater than or equal to 160 mm Hg. Trials in resistant hypertension with systolic BP 140 mm Hg to 160 mm Hg are planned.

Are the benefits long lasting? Are there renal risks that become apparent several years after denervation? Patients in non–U.S. studies were followed for 3 years, with sustained BP response and kidney function. An ongoing U.S. trial will follow patients for 5 years, and a postmarketing registry will be an FDA requirement.

Can the results in relatively homogeneous non–U.S. populations be generalized to patients in the United States? Presumably, ongoing and planned studies in the United States will reflect our racial/ethnic and clinical diversity.

Will renal nerves regenerate after radioablation? From transplant experience we know that, to some extent, renal nerves grow back. Although 3-year follow-up after denervation in a limited number of patients suggests persistent BP effects, additional information will be available from ongoing and planned studies, which are longer and larger.

Will the cost of denervation be offset by savings in prescription drugs, outpatient visits, hypertension-related

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