Editorial Commentary

Can Physiology Zap Therapeutic Sweet Spots in Hypertension?

Michael J. Joyner

See related article, pp 1485–1490

Resistant hypertension is a vexing medical problem. It is defined as poorly controlled blood pressure in spite of treatment with optimal doses of ≥3 different classes of drugs.1 In this context, the archetypal patient with resistant hypertension is an obese person in late middle age who might or might not have coexisting diseases, such as diabetes mellitus, peripheral vascular disease, and mildly impaired ventricular function or diastolic dysfunction. A blood pressure value of 150 to 160/95 mm Hg or greater would not be uncommon, and such a value puts these individuals at markedly increased risk for heart attack and stroke.

So, the question is what to do about these difficult-to-treat patients? Although many of these patients might respond to truly intensive multimodal lifestyle modification, this has been difficult to implement in a widespread way in real populations.2 Our obesogenic modern world is also a blood pressure–raising one. In this context, device therapy, most notably catheter-based renal denervation (also called renal nerve ablation), has moved to fill this therapeutic breach.3

How Does Renal Denervation Work?

There are 2 basic theories about how renal denervation might lower arterial pressure. First, a reduction in sympathetic activity to the kidney will limit activation of the renin-angiotensin-aldosterone system and blunt the vicious blood pressure–raising cycle seen when this system is activated. A second idea is that in at least some patients with resistant hypertension inflammation or some other stimulus is activating blood pressure–raising renal afferents, which in turn evoke increases in sympathetic activity. There is at least some evidence in support of both concepts, and emerging ideas have stressed the role of sympathexcitatory renal afferents in hypertension.4

Does Renal Denervation Reduce Sympathetic Activity?

In this issue of Hypertension, Brinkmann et al5 used what might be described as a suite of high-resolution phenotyping and physiology techniques and measured blood pressure and muscle sympathetic nerve activity before and after renal denervation in 12 subjects with resistant hypertension. In contrast to the larger clinical trials and some early reports, they found no reduction in blood pressure 3 to 6 months after renal denervation and no reductions in sympathetic activity. This latter finding is especially important because there is at least some evidence suggesting a major role for chronically elevated efferent sympathetic vasoconstrictor outflow in resistant hypertension.6

These new data raise a number of important general and specific issues related to device therapy for resistant hypertension. First, there is the issue of patient selection. Assuming these techniques work in at least some patients, how best to identify the subsets of patients who are either likely or unlikely to respond to this intervention? Second, is it possible that patients reported in this article were not or were inadequately denervated? Is there some way to ensure adequate denervation at the time of ablation? Third, hypertension studies are notoriously difficult to conduct, especially in complex patients, because blood pressure–lowering effects of any new therapy might be overshadowed or missed simply by increased compliance in the control group. And finally, is the standard placebo-controlled trial the best way to go in these types of complex patients?

High-Resolution Physiological Phenotyping to Find Therapeutic Sweet Spots?

In addition to the specific questions that this article raises about renal denervation, there are larger issues related to the adoption of high-tech medical technology and a tendency for soft indications and expanded use (indication creep) that might or might not be justified over time.7 A recent example that has received attention in the popular press might be described as the appropriate use and subsequent overuse of erythropoietin to treat anemia in selected patients.8,9 What started out as a niche triumph for biotechnology and a niche compound to treat transfusion-dependent renal failure patients expanded over the years in ways that added great cost but questionable benefit to the healthcare system in the United States. Importantly, what is the role of high-resolution phenotyping and human physiology experiments in small groups of patients? In addition to clinical end points, integrative physiological data may be necessary to understand if, how, and why these therapies are working. Might studies using classical clinical research center approaches help identify therapeutic sweet spots for promising new technologies and drugs? Has the transition of the National Institutes of Health–funded General Clinical Research Centers system to the Clinical and Translational Science Awards damaged this critical capability in the United States?20 Will the emergence of the National Center for Advancing Translational Science degrade it further?11

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From the Department of Anesthesiology, Mayo Clinic, Rochester, MN.

Correspondence to Michael J. Joyner, Department of Anesthesiology, Mayo Clinic, 200 First St SW, Rochester, MN 55905. E-mail: joyner.michael@mayo.edu

(Hypertension. 2012;60:1385-1386.)

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Hypertension is available at http://hyper.ahajournals.org

DOI:10.1161/HYPERTENSIONAHA.112.202754
What’s Old Is New Again?

At some level, catheter-based renal denervation is a distant relative of various forms of surgical sympathectomy that were used in the predrug era to treat hypertension. Renal denervation is also not the only device therapy for hypertension that is emerging. Carotid sinus nerve stimulation to evoke reflex reductions in blood pressure is also being studied as means to treat resistant hypertension. This approach also revivifies ideas from an earlier era, and many of the same questions about patient selection and indication creep also apply to it. Whatever the fate of these specific technologies, we would all do well to remember that the early and dramatic drug trials in hypertension used drugs that might be called sympatholytic. Perhaps more thought about how to modulate the sympathetic nervous system in human hypertension is needed, as well as determining how to preserve the ability of the research community to do the physiologically based phenotyping in humans that is necessary to find therapeutic sweet spots for complex diseases.

Sources of Funding

This work was supported by National Institutes of Health grant HL 83947.

Disclosures

None.

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Hypertension. 2012;60:1385-1386; originally published online October 8, 2012; doi: 10.1161/HYPERTENSIONAHA.112.202754

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