EDITORIAL

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Renal denervation: Are we on the right path?

When renal sympathetic denervation, an endovascular procedure designed to treat resistant hypertension, failed to meet its efficacy goal in the SYMPLICITY HTN-3 trial,[1] the news was disappointing.

See related article, page 681

In this issue of the *Cleveland Clinic Journal of Medicine*, Shishehbor et al[2] provide a critical review of the findings of that trial and summarize its intricacies, as well as the results of other important trials of renal denervation therapy for hypertension. To their excellent observations, we would like to add some of our own.

HYPERTENSION: COMMON, OFTEN RESISTANT

The worldwide prevalence of hypertension is increasing. In the year 2000, about 26% of the adult world population had hypertension; by the year 2025, the number is projected to rise to 29%—1.56 billion people.[3]

Only about 50% of patients with hypertension are treated for it and, of those, about half have it adequately controlled. In one report, about 30% of US patients with hypertension had adequate blood pressure control.[4]

Patients who have uncontrolled hypertension are usually older and more obese, have higher baseline blood pressure and excessive salt intake, and are more likely to have chronic kidney disease, diabetes, obstructive sleep apnea, and aldosterone excess.[5] Many of these conditions are also associated with increased sympathetic nervous system activity.[6]

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Resistance and pseudoresistance

But lack of control of blood pressure is not the same as resistant hypertension. It is important to differentiate resistant hypertension from *pseudoresistant* hypertension, ie, hypertension that only seems to be resistant.[7] Resistant hypertension affects 12.8% of all drug-treated hypertensive patients in the United States, according to data from the National Health and Nutrition Examination Survey.[8]

Factors that can cause pseudoresistant hypertension include:

- Suboptimal antihypertensive regimens (truly resistant hypertension means blood pressure that remains high despite concurrent treatment with 3 antihypertensive drugs of different classes, 1 of which is a diuretic, in maximal doses)
- The white coat effect (higher blood pressure in the office than at home, presumably due to the stress of an office visit)
- Suboptimal blood pressure measurement techniques (eg, use of a cuff that is too small, causing falsely high readings)
- Physician inertia (eg, failure to change a regimen that is not working)
- Lifestyle factors (eg, excessive sodium intake)
- Medications that interfere with blood pressure control (eg, nonsteroidal anti-inflammatory drugs)
- Poor adherence to prescribed medications.

Causes of secondary hypertension such as obstructive sleep apnea, primary aldosteronism, and renal artery stenosis should also be ruled out before concluding that a patient has resistant hypertension.

The SYMPLICITY HTN-3 trial did not meet its primary efficacy end points

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Treatment prevents complications

Hypertension causes a myriad of medical diseases, including accelerated atherosclerosis, myocardial ischemia and infarction, both systolic and diastolic heart failure, rhythm problems (eg, atrial fibrillation), and stroke.

Most patients with resistant hypertension have no identifiable reversible causes of it, exhibit increased sympathetic nervous system activity, and have increased risk of cardiovascular events. The risk can be reduced by treatment.[9,10]

Adequate and sustained treatment of hypertension prevents and mitigates its complications. The classic Veterans Administration Cooperative Study in the 1960s demonstrated a 96% reduction in cardiovascular events over 18 months with the use of 3 antihypertensive medications in patients with severe hypertension.[11] A reduction of as little as 2 mm Hg in the mean blood pressure has been associated with a 10% reduction in the risk of stroke mortality and a 7% decrease in ischemic heart disease mortality.[12] This is an important consideration when evaluating the clinical end points of hypertension trials.

Resistant hypertension must be differentiated from pseudoresistant hypertension

SYMPLICITY HTN-3 TRIAL: WHAT DID WE LEARN?

As controlling blood pressure is paramount in reducing cardiovascular complications, it is only natural to look for innovative strategies to supplement the medical treatments of hypertension.

The multicenter SYMPLICITY HTN-3 trial[1] was undertaken to establish the efficacy of renal-artery denervation using radiofrequency energy delivered by a catheter-based system (Symplicity RDN, Medtronic, Dublin, Ireland). This randomized, sham-controlled, blinded study did not show a benefit from this procedure with respect to either of its efficacy end points—at 6 months, a reduction in office systolic blood pressure of at least 5 mm Hg more than with medical therapy alone, or a reduction in mean ambulatory systolic pressure of at least 2 mm Hg more than with medical therapy alone.

Despite the negative results, this medium-size (N = 535) randomized clinical trial still represents the highest-level evidence in the field, and we ought to learn something from it.

Limitations of SYMPLICITY HTN-3

Several factors may have contributed to the negative results of the trial.

Patient selection. For the most part, patients enrolled in renal denervation trials, including SYMPLICITY HTN-3, were not selected on the basis of heightened sympathetic nervous system activity. Assessment of sympathetic nervous system activity may identify the population most likely to achieve an adequate response.

Of note, the baseline blood pressure readings of patients in this trial were higher in the office than on ambulatory monitoring. Patients with white coat hypertension have increased sympathetic nervous system activity and thus might actually be good candidates for renal denervation therapy.

Adequacy of ablation was not measured. Many argue that an objective measure of the adequacy of the denervation procedure (qualitative or quantitative) should have been implemented and, if it had been, the results might have been different. For example, when ablation is performed in the main renal artery as well as the branches, the efficacy in reducing levels of norepinephrine is improved.[13]

Blood pressure fell in both groups. In SYMPLICITY HTN-3 and many other renal denervation trials, patients were assessed using both office and ambulatory blood pressure measurements. The primary end point was the office blood pressure measurement, with a 5-mm Hg difference in reduction chosen to define the superiority margin. This margin was chosen because even small reductions in blood pressure are known to decrease adverse events caused by hypertension. Notably, blood pressure fell significantly in both the control and intervention groups, with an intergroup difference of 2.39 mm Hg (not statistically significant) in favor of denervation.

Medication questions. The SYMPLICITY HTN-3 patients were supposed to be on stable medical regimens with maximal tolerated doses before the procedure. However, it was difficult to assess patients' adherence to and tolerance of medical therapies. Many (about 40%) of the patients had their medications changed during the study.[1]

Therefore, a critical look at the study enrollment criteria may shed more light on the

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reasons for the negative findings. Did these patients truly have resistant hypertension? Before they underwent the treatment, was their prestudy pharmacologic regimen adequately intensified?

ONGOING STUDIES

After the findings of the SYMPLICITY HTN-3 study were released, several other trials—such as the Renal Denervation for Hypertension (DENERHTN)[14] and Prague-15 trials[15]—reported conflicting results. Notably, these were not sham-controlled trials.

Newer studies with robust trial designs are ongoing. A quick search of www.clinicaltrials.gov reveals that at least 89 active clinical trials of renal denervation are registered as of the date of this writing. Excluding those with unknown status, there are 63 trials open or ongoing.

Clinical trials are also ongoing to determine the effects of renal denervation in patients with heart failure, atrial fibrillation, sleep apnea, and chronic kidney disease, all of which are known to involve heightened sympathetic nervous system activity.

NOT READY FOR CLINICAL USE

Although nonpharmacologic treatments of hypertension continue to be studied and are supported by an avalanche of trials in animals and small, mostly nonrandomized trials in humans, one should not forget that the SYMPLICITY HTN-3 trial simply did not meet its primary efficacy end points. We need definitive clinical evidence showing that renal denervation reduces either blood pressure or clinical events before it becomes a mainstream therapy in humans.

Additional trials are being conducted that were designed in accordance with the recommendations of the European Clinical Consensus Conference for Renal Denervation[16] in terms of study population, design, and end points. Well-designed studies that conform to those recommendations are critical.

Finally, although our enthusiasm for renal denervation as a treatment of hypertension is tempered, there have been no noteworthy safety concerns related to the procedure, which certainly helps maintain the research momentum in this field.

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