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# The promise of renal denervation

**R**ESISTANT HYPERTENSION HAS BECOME the focus of intense medical interest. The most commonly accepted definition of resistant hypertension is uncontrolled blood pressure despite the use of drugs from three or more antihypertensive classes, one of which is a diuretic, at maximally tolerated doses. About 1 in 50 patients with a new diagnosis of hypertension will develop resistant hypertension.<sup>1</sup>

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In the 1950s, surgical renal denervation was shown to be a highly effective treatment for resistant hypertension, but the procedure was abandoned because of intolerable side effects such as bladder dysfunction and orthostasis. More recently, carotid baroreceptor surgery for resistant hypertension was investigated; results were encouraging, but this currently remains a surgical procedure.<sup>2</sup> Now, catheter-based renal denervation has emerged as a potential minimally invasive strategy to treat resistant hypertension.

In this issue of *Cleveland Clinic Journal of Medicine*, Thomas et al provide an elegant review of catheter-based renal denervation to treat resistant hypertension.<sup>3</sup> The authors nicely summarize the available data for renal denervation for resistant hypertension. A reduction in office systolic blood pressure of about 30 mm Hg has been observed.<sup>4,5</sup> In the

published studies to date, there have been no major complications beyond those associated with any angiographic procedure.

Of note, this procedure is investigational in the United States, though it is available outside of research studies in other parts of the world. Symplicity HTN-3, a pivotal trial for potential US Food and Drug Administration approval of catheter-based renal denervation, is ongoing.<sup>6</sup>

The review by Thomas et al is relevant to primary care physicians, cardiologists, nephrologists, and endocrinologists, all of whom manage patients with resistant and refractory hypertension. It explains the potential indications and referral patterns for the procedure, if approved. This review brings clinicians quickly up to speed about the exciting developments in renal denervation.

## ■ UNANSWERED QUESTIONS

As should be evident, there are many unanswered questions about renal denervation.

The long-term durability of catheter-based renal denervation remains to be determined. The available data support a sustained effect out to at least 2 years.<sup>7</sup> Further study will be necessary to determine if there are some patients in whom the effects wear out over time. But even if that happens, assuming the beneficial effect lasts at least a few years, it may be reasonable to repeat the procedure.

Another important question is whether the reductions in blood pressure with denervation translate into reductions in stroke, heart failure, renal failure, myocardial infarction, and death. It is logical to think that this relationship holds for catheter-based denervation as it does for medical therapy, though more study is needed to see if this is true.

Only with further careful randomized trials of renal denervation will its full promise be realized

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Dr. Bakris has disclosed that he has received research grants from Forest Labs, Relapsya, and WebMD and has served as a consultant to Abbott, Takeda, Johnson & Johnson, Daiichi-Sankyo, and Medtronic. He serves as the co-principal investigator of the Symplicity HTN-3 trial, which is sponsored by Medtronic.

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## ■ CAVEATS

As with coronary artery disease, it will be important to ensure that patients labeled as having resistant hypertension truly have the disease. The diagnosis requires a careful history, evaluation of potential causes of secondary hypertension, and increased use of ambulatory blood pressure monitoring to rule out white-coat and masked hypertension.

If a patient truly has resistant hypertension, appropriate lifestyle modifications (primarily salt restriction to levels well below 2.4 g/day) and aggressive pharmacotherapy should first be attempted.<sup>8</sup> Aldosterone blockade clearly has an important role, especially in obese patients, as it has been shown to markedly lower blood pressure in this phenotype.<sup>9</sup>

Imitation is the greatest form of flattery, and this is certainly true in the world of drugs and medical devices. Accordingly, a number of systems for renal denervation are being developed. This will likely spur further innovation and refinement in the technology.

On the other hand, as with coronary artery stents, it is important to realize that there is a fair amount of engineering sophistication behind catheter-based renal denervation. As has already happened in some parts of the world, taking a radiofrequency catheter designed for electrophysiology procedures and indiscriminately using it for renal denervation could be dangerous for patients.

Furthermore, if practitioners rapidly adopt this procedure but do not adhere to the indications and protocols used in the clinical trials, the outcomes could be worse, and the net

result might be a setback for this promising field of research.

## ■ OTHER INDICATIONS AND BENEFITS?

As Thomas et al point out, in addition to resistant hypertension, renal denervation has also been studied in heart failure, chronic renal failure, diabetes mellitus, and sleep apnea.<sup>10–12</sup> Sympathetic nerve overactivity appears to have a pathologic role in all these diseases. In small studies, renal denervation has already been shown to improve systolic and diastolic dysfunction, to cause regression of left ventricular hypertrophy, and to improve glycemic control. Since these cardiovascular risk factors often cluster in the same patient, a treatment that addresses several risk factors simultaneously would be expected to have a profound benefit on cardiovascular outcomes, though this remains to be established.

Several studies are under way. Symplicity-HF will study renal denervation in 40 patients with chronic heart failure and renal impairment. The Symplicity registry will follow more than 5,000 patients undergoing catheter-based renal denervation for resistant hypertension and other conditions marked by sympathetic nerve overactivity. If an important role for renal denervation is validated in Symplicity HTN-3, it would be easy to imagine trials of renal denervation in patients with lesser degrees of hypertension.

Only with further careful randomized trials of renal denervation will its full promise be realized.

**If a patient truly has resistant hypertension, lifestyle modifications and aggressive drug therapy should be tried first**

## ■ REFERENCES

1. Daugherty SL, Powers JD, Magid DJ, et al. Incidence and prognosis of resistant hypertension in hypertensive patients. *Circulation* 2012; e-pub ahead of print.
2. Bisognano JD, Bakris G, Nadim MK, et al. Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: results from the double-blind, randomized, placebo-controlled Rheos Pivotal Trial. *J Am Coll Cardiol* 2011; 58:765–773.
3. Thomas G, Shishebor MH, Bravo EL, Nally JV. Renal denervation to treat resistant hypertension. *Cleve Clin J Med* 2012; 79:501–510.
4. Krum H, Schlaich M, Whitbourn R, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet* 2009; 373:1275–1281.
5. Symplicity HTN-2 Investigators; Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Böhm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. *Lancet* 2010; 376:1903–1909.
6. Kandzari DE, Bhatt DL, Sobotka PA, et al. Catheter-based renal denervation for resistant hypertension: rationale and design of the SYMPPLICITY HTN-3 Trial. *Clin Cardiol* 2012; in press.
7. Symplicity HTN-1 Investigators. Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. *Hypertension* 2011; 57:911–917.
8. Chobanian AV, Bakris GL, Black HR, et al; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detec-

- tion, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003; 42:1206–1252.
9. **Calhoun DA, Jones D, Textor S, et al; American Heart Association Professional Education Committee.** Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Circulation 2008; 117:e510–e526.
  10. **Mahfoud F, Schlaich M, Kindermann I, et al.** Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: a pilot study. Circulation 2011; 123:1940–1946.
  11. **Brandt MC, Mahfoud F, Reda S, et al.** Renal sympathetic denervation reduces left ventricular hypertrophy and improves cardiac function in patients with resistant hypertension. J Am Coll Cardiol 2012; 59:901–909.
  12. **Witkowski A, Prejbisz A, Florczak E, et al.** Effects of renal sympathetic denervation on blood pressure, sleep apnea course, and glycemic control in patients with resistant hypertension and sleep apnea. Hypertension 2011; 58:559–565.
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