EDITORIAL COMMENT

Anatomical Exclusion for Renal Denervation

Are We Putting the Cart Before the Horse?*

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The race is underway to develop a safe and widely applicable endovascular solution for renal sympathetic denervation (RDN). Important limitations of first-generation RDN devices have spurred innovative new solutions in the form of unique endovascular technologies, including many that are currently under investigation in clinical trials (1). Certainly, these developments add encouragement to the provocative, if not limited, randomized treatment results of the SYMPLICITY HTN-2 (Renal Sympathetic Denervation in Patients With Treatment-Resistant Hypertension) trial (2). Even if further randomized clinical experience strengthens the concept of RDN, there remain important considerations that are likely to limit broader application of this technology.

Among other restrictions, renal anatomy must be favorable to permit satisfactory treatment delivery. Specifically, the current iteration of most catheter-based RDN systems require a renal artery diameter of $\geq 4$ mm ($\geq 3$ mm for Vessix, Boston Scientific, Inc., Natick, Massachusetts), a treatable vessel length of $\geq 20$ mm, and no significant accessory arterial branches (supplying more than 25% of blood flow) to the kidney. Renal artery anatomy can be quite variable and may limit applicability of RDN if current anatomic eligibility requirements do not change with improvements in technology. Indeed, nearly 16% of the 190 patients screened in the SYMPLICITY HTN-2 trial were excluded based on anatomic criteria alone (2).

In this issue of JACC: Cardiovascular Interventions, Rimoldi et al. (3) present an observational analysis of 934 consecutive subjects with resistant and nonresistant hypertension who underwent renal angiography at the discretion of their provider. Angiographic results were categorized by definitions of anatomic eligibility according to current renal denervation trials using the Symplicity catheter system (Medtronic, Mountain View, California). A group of 8 experienced physicians performed quantitative measurements of the renal artery diameter and vessel length, among whom the investigators report a reasonably low level of intra- and inter-reader variability (3).

Among 934 subjects undergoing renal angiography, 90 (9.6%) patients were excluded due to renal artery stenosis. Of the remaining 844 eligible patients, only 443 (52%) had vascular anatomy suitable for RDN. The most common exclusion from RDN eligibility was vessel length $<20$ mm (25%) due to early renal artery bifurcation, followed by accessory renal arteries (19%), and renal artery diameter $<4$ mm (15%). Among the 117 patients retrospectively identified to have resistant hypertension, anatomic eligibility for renal denervation was 53%. Interestingly, the investigators found no differences in eligibility rates based on whether or not the patient had resistant or nonresistant hypertension.

This study highlights the anatomic limitations of current catheter-based renal denervation techniques, but a few points deserve further discussion. First, most renal denervation trials allow accessory renal arteries as long as these do not perfuse $>25\%$ of the ipsilateral renal parenchyma (4). Whereas some devices (Vessix) allow ablation of these vessels if the diameter is $>3$ mm, current European consensus documents advocate the absence of polar or accessory renal arteries (5). Furthermore, a recent small study showed a significantly lesser reduction in blood pressure in those patients with multiple renal arteries versus patients with a single main artery (6). The impact of accessory or polar renal arteries on catheter-based renal denervation remains under investigation. Second, the current randomized trials have excluded eligible vessel length of $<20$ mm, however, most clinical trials allow side branches if the diameter of these vessels is $<50\%$ of the main renal artery (4). Furthermore, with newer generation multielec- trode devices, it is not clear whether $20$ mm of eligible vessel length is actually necessary. Currently, there is little corre- lation between the number of ablation sites and reduction in blood pressure. Therefore, much shorter ablation length may be adequate in the near future. Third, prior to renal angiography, vasodilatory medications were not adminis- tered, something that is currently required by most clinical trials (4). Fourth, the investigators excluded any renal artery stenosis (according to the European consensus); however, most trials allow some degree of renal atherosclerosis ($<30\%$ to $50\%$) (4,5).

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In summary, renal and carotid catheter-based therapies to treat hypertension and other conditions such as atrial fibrillation, ventricular tachycardia, pulmonary hypertension, metabolic syndrome, and sleep apnea, among others, are rapidly under development (7). It is exciting to learn about the current limitations of catheter-based renal denervation devices; however, we must remain cautious about putting the cart before the horse when the safety and efficacy of these interventions has yet to be determined. Indeed, despite a high prevalence of resistant or uncontrolled hypertension, published data are available only on 100 patients worldwide who have ever been randomized (SYMPLICITY HTN-2) to renal denervation versus control group (2). Furthermore, despite limited level 1 data, there have been 2 expert consensus documents related to catheter-based renal denervation, and 4 devices have already gained European approval and are clinically available outside the United States (5,8)! Clearly, there is much we must learn before widespread use of catheter-based renal denervation.

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