

EDITORIAL COMMENT

Catheter-Based Renal Denervation

The Black Box Procedure*

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Catheter-based renal denervation (RDN) has evolved recently as a promising minimally invasive treatment for patients with hypertension, based on the concept of an old surgical technique (1). RDN has been shown to reduce renal norepinephrine spillover (2), muscle sympathetic nerve activity (3), office systolic and diastolic blood pressure in patients with severe and less severe resistant hypertension (4–6), to improve diastolic function and reduce left ventricular mass index (7), without negatively affecting renal function (8) or causing chronotropic incompetence during cardiopulmonary exercise testing (9). RDN may be used not only to treat hypertension, but also several metabolic and cardiovascular diseases that are characterized by high sympathetic activity (10), such as diabetes and hyperinsulinemia (11), heart failure (12), arrhythmias (13), and chronic kidney disease (14).

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The potential of RDN is enormous and given the large number of patients affected by hypertension worldwide, the development of technology and industry interest have increased rapidly. Up until today, approximately 10,000 patients around the world underwent RDN in clinical practice, most of them with the Symplicity device (Medtronic, Mountain View, California) (15). The selection of appropriate patients is key to ensuring successful treatment, and prediction of treatment response has remained elusive (16,17). Blood pressure response after RDN varies, and in up to 40% of patients, only minor or no blood pressure changes are achieved (non-response). The definition of non-response in the context of RDN was introduced for the first time in the Symplicity trials (4,18). Arbitrarily, it has been defined as a reduction of office systolic blood pressure of <10 mm Hg after six months following RDN, representing a clinically meaningful threshold for drop in blood pressure. In previously published studies, the rate of non-response after RDN ranged between 8–17% and was 37% in the crossover group of Symplicity HTN-2 trial (18). The causes of non-response are not yet fully understood and include: 1) inappropriate patient selection (e.g., prevalence of secondary hypertension); 2) minor contribution of the sympathetic nervous system to the expression of hypertension; 3) changes of antihypertensive medication and non-adherence after the procedure; and 4) ineffective RDN procedure (19). The latter is especially important for interventionalists performing the procedure.

Already in 2013, six RDN systems using different treatment strategies have received European approval (CE mark): Medtronic's Symplicity system, St. Jude's EnligHTN system, Vessix's V2 system, Covidien's One Shot system, Terumo's Iberis system and Recor's Paradise system (16). Except for the ultrasound-based Recor's Paradise system, most of these devices use radiofrequency energy to target renal sympathetic nerves. The devices differ concerning the delivered energy, number of electrodes, design of the catheter, type of energy delivery, and duration of ablation. Although crucial from an interventionalist's perspective, the major unresolved issue is how to monitor treatment success intraprocedurally, as blood pressure changes rarely occur directly after the procedure but rather may take weeks to months. Any currently available device has yet not addressed this issue. The available systems display different parameters including temperature, power, ablation time, impedance and drop in impedance during energy delivery compared with baseline. Some of the systems even allow changing energy output and ablation time. Interestingly, very little has been published on pre-clinical experience and none of the settings have been confirmed by pre-clinical studies available in the public domain, although several pre-clinical studies have been performed and presented during congresses, such as this year's EuroPCR in Paris. Inevitably, several questions arise while performing RDN procedures:

1. What are normal values for impedance in renal arteries, and can the baseline impedance be used finding good ablation spots?
2. Is a higher temperature, longer ablation time or greater impedance drop during treatment associated with better outcome?
3. Do the number of ablations correlate to blood pressure response after treatment?
4. What to do in patients with dual renal arteries, polar arteries or small vessels (<4 mm)?

Inappropriate renal artery anatomical conditions for percutaneous RDN therapy have been defined as previous renal artery intervention (balloon angioplasty or stenting), evidence of renal artery atherosclerosis (defined as a renal artery stenosis >50%), main renal arteries of <4 mm in diameter or <20 mm in length or presence of multiple main renal arteries in either kidney (16). Patients with the aforementioned anatomy have been excluded from most of the published studies.

In this issue of *JACC: Cardiovascular Interventions*, Id et al. (20) report the results of a retrospective, single-center analysis on the efficacy of RDN in patients with bilateral single renal arteries (defined as optimal anatomy) and patients with accessory arteries (defined as suboptimal anatomy). In this valuable study, a total of 74 patients with resistant hypertension were included, 54 (73%) had single renal arteries and 20 (27%) accessory renal arteries. Overall the office blood pressure lowering after six months (-17/-7 mm Hg) was slightly less compared with previously published studies (16), which could be related to both the higher baseline blood pressure and the exclusion of patients with accessory renal arteries in those trials. Of the 20 patients with accessory renal arteries, 9 underwent RDN of all arteries with diameter >3.5 mm and 11 were treated incompletely. In patients with accessory renal arteries and incomplete RDN, blood pressure reductions were less pronounced compared with patients with optimal anatomy. The authors concluded that ablation of accessory arteries of >3.5 mm appears to be safe and complete denervation should be attempted whenever possible. However, one should keep in mind that the patients did not undergo rigorous routine renal artery imaging (by CT or MRI) during follow-up, and given the fact that especially small renal arteries (<4 mm) tend to develop severe spasms after radiofrequency ablation, renal artery stenosis or flow limiting obstruction could have been missed during follow-up. The paper provides new insights into the prevalence of accessory arteries (27%) in patients with resistant hypertension considered for RDN and their role in blood pressure regulation. Yet, before definitive statements regarding the importance of complete and incomplete denervation in accessory renal arteries can be made, the findings need to be confirmed in a larger set of patients (as the numbers of

patients in the subgroups were limited) with extended follow-up examinations, including ambulatory blood pressure monitoring and proper renal artery imaging.

Device companies and investigators should be strongly encouraged to publish their pre-clinical data in order to provide interventionalists with necessary information. This includes very basic information such as the effectiveness of catheter-based RDN compared with surgical sympathectomy in reducing renal norepinephrine tissue content, predictability of renal nerve damage and potential nerve regrowth after RDN. Future clinical studies should meticulously investigate the relevance and predictive value of different procedural parameters, such as number of ablations, temperature, power, and impedance on blood pressure lowering. For the time being, treating physicians have to accept a black box during the procedure, knowing that for certain patients it works, but not entirely sure just how.

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