MAYO CLINIC

Revisiting Renal Denervation

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The initial publication reviewing the effects of catheter-based renal denervation (RDN) in humans appeared in 2009. This open-label, nonrandomized, proof-of-principle study observed office blood pressure reductions of 22 mm Hg systolic and 11 mm Hg diastolic in drug-resistant hypertensive patients consuming an average of approximately 5 medications daily after 6 months of follow-up.[1] One year later, a second study in 2010 reported a similar reduction in office blood pressures in the setting of a larger, unblinded, randomized trial.[2]

In the interval years between 2010 and the publication of the HTN-3 trial in 2014, meta-analyses appeared that testified with enthusiasm to the impressive blood pressure (BP) reduction associated with RDN therapies, irrespective of catheter type, generally ending with a note of caution about the need for a large, randomized, blinded and properly controlled trial.[3,4]

After these successful experiences, a sham-controlled, randomized, and blinded trial was initiated in the United States.[5] This trial included a sham control group that underwent the denervation procedure (catheterization laboratory, conscious sedation, angiography) except for the actual denervation itself. When compared with the RDN group, the sham control group lowered blood pressure to almost the same degree, whether measured in the office or by ambulatory blood pressure monitoring, in drug-resistant hypertensive patients.[6] This trial's disappointing results cast considerable doubt on the value of this approach in managing this difficult patient population.[7] An editorial in the *British Medical Journal* that appeared shortly after the results of HTN-3 were announced captured the issue of bias in the studies leading up to HTN-3,[8] and we returned to the drawing board and began an in-depth postmortem examination of the results. After months of interaction with multiple experts in hypertension, cardiology, and biostatistics, several areas of trial design were identified that were believed to have contributed to the disappointing results.[9] This was also an opportunity to lay to rest the question of whether RDN really does anything to lower the blood pressure in the untreated state (no antihypertensive medication), and whether an effect on blood pressure (if present) was evident in the presence of antihypertensive medication. This opportunity led to the twin pilot studies called the HTN-OFF MED and HTN-ON MED trials,[10] which were both initiated in 2015. Each of these pilot studies showed encouraging results using 24-hour ambulatory systolic BP as the outcome.[11,12] Although the majority of companies initially invested in this approach to hypertension pulled out after HTN-3, a few device companies persisted, and they form the core group leading the present investigations in this area.

In this issue of the *Proceedings*, an update on the field is presented that incorporated the results of 12 randomized clinical trials of RDN undertaken with either radiofrequency ablation or by ultrasound presented by Cheng et al.[13] The authors note that the RDN procedure, compared with the control group, is associated with an ambulatory systolic BP reduction of 4 mm Hg over 24 hours, and an in-office systolic BP reduction of 9 mm Hg, after approximately 5 months of follow-up. Importantly, their review also covered the safety of RDN, which is in line with other percutaneous interventions using the femoral artery, and similar between the RDN and the sham control groups. Their analysis complements further the growing consensus of what is likely to be the true systolic BP change in the post–HTN-3 era. In a nutshell, RDN appears to have efficacy similar to many drug monotherapies used in treating hypertension,[14] particularly in those whose starting office systolic BP is in the range of 150-160 mm Hg.

Responding to the increasing accumulation of data in RDN studies, the US Food and

Drug Administration convened a panel to advise them on aspects of study design and interpretation for device-based antihypertensive therapies in an open meeting on December 5, 2018 (https://www.fda.gov/AdvisoryCommittees/Calendar/ucm624402.htm). During that meeting Medtronic, Recor, ROX Medical, and Vascular Dynamics all presented data on the efficacy and safety of device-based approaches to hypertension care. This represented the broad spectrum of:

- Radiofrequency ablation in the main kidney arteries and the early branch vessels (Medtronic; SPYRAL Catheter)
- Ultrasound ablation in the main kidney arteries (Recor; Paradise System)
- An iliac arteriovenous fistula device (ROX Coupler; ROX Medical; currently, ROX studies are not active)
- A unilateral, internal carotid artery, baroreflex amplification stent device (MobiusHD; Vascular Dynamics)

At the time of this writing (June 2019), it is likely that device-based antihypertensive treatments are still at least 1 year away from submission for US Food and Drug Administration review and approval. In the meantime, several issues are becoming clearer, and several issues remain to be refined, as investigation into the device-based approaches to hypertension care continues.

Clarity issues include the duration of effect and overall safety. With the establishment of a renal denervation registry,[15] approximately 3000 individuals from around the world will be followed after receiving RDN. The registry data suggest that the procedure maintains a lowered blood pressure for at least 3 years. In addition, the registry data show stable renal function over time, supporting the periprocedural safety issues noted by Cheng et al[13] in this issue.

Areas under scrutiny include optimal patient selection and verification of effective renal denervation. In the recent radiofrequency ablation trials[11,12] and the ultrasound ablation trial,[16] approximately 1 in 3 people treated with RDN have a systolic BP reduction less than 5 mm Hg overs 24 hours systolic and could be considered "nonresponders." At this time, there is no way known to predict accurately who will or will not respond to kidney artery nerve ablation. Moreover, after RDN is performed it takes a minimum of 2 (ultrasound energy) or 3 (radiofrequency energy) months to see a denervation reduction in systolic BP "signal." Unlike coronary artery intervention, in which the catheter-based intervention results in an immediate cosmetic change in the appearance of an atherosclerotic lesion, there is no reliable way to assess the adequacy of kidney nerve ablation during the procedure itself.

The lessons from the past are the importance of study design and adherence to the protocol. The challenges for the future will be to determine which patients will respond best to RDN, and how to ensure successful denervation. The contribution of Cheng et al[13] in this issue provides additional assurance that renal artery denervation represents a viable technique to lower blood pressure in hypertensive patients.

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