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Letters

TO THE EDITOR

Chemical Renal Denervation Revisited

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We read with great interest the report by Fischell et al. (1), presenting the first-in-human experience with transcatheter alcohol-mediated perivascular renal denervation using the Peregrine system. This study proved the safety and feasibility of chemical renal sympathetic denervation using microdoses of alcohol infused via microneedles into the perivascular space of the renal artery.

Despite the discouraging early results of the sham-controlled SYMPLICITY HTN-3 trial, renal denervation still offers great interest, as it deals with patients who have no other option for the treatment of resistant hypertension. Chemical renal artery denervation was first introduced (2) by our group with vincristine, a vinca alkaloid antineoplastic drug that inhibits deoxyribonucleic acid and ribonucleic acid synthesis and its potent neurotoxicity by causing giant axonal swellings and secondary demyelination, which has been used both in an experimental model (3) and in humans with resistant hypertension (4,5). In an experimental model, its local delivery by a dedicated catheter showed favorable outcomes regarding a decrease in the number of renal sympathetic nerves, leading to the assumption that this method can be used effectively to treat resistant hypertension (3,4). This was proved in the first-in-human application of chemical denervation by vincristine, which was safe and resulted in a significant decrease in systolic blood pressure in a patient with resistant hypertension (5).

The recently published data on the use of alcohol denervation are encouraging and may increase interest in chemical denervation as an alternative to radiofrequency renal denervation in specific populations.

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REPLY: Chemical Renal Denervation Revisited

It is our pleasure to respond to the letter published by Dr. Toutouzas and colleagues in reference to our paper describing the first-in-human experience with the Peregrine System for chemical renal denervation (RDN) (1). We appreciate their enthusiasm for the concept and acknowledge their contributions in this space using the local delivery of vincristine to perform chemical RDN (2).

As pointed out in their letter, the failure of the sham-controlled SYMPLICITY HTN-3 trial (3) left many observers with a bias that RDN has failed. We agree with Toutouzas and colleagues, and others, that there is still promise for RDN but that the flaws in the SYMPLICITY HTN-3 trial made it challenging to demonstrate a therapeutic effect. Factors that may have contributed to the failure of that trial include: 1) a lack of operator experience, with no run-in procedures to allow the physicians to learn how to use the device properly; 2) a lack of adequate denervation due to challenges in

achieving adequate depth and circumferential ablation using RF energy; 3) inadequate number and spatial orientation of ablations; and 4) challenges in controlling drug compliance, as well as the addition of antihypertensive medications during the study period (4).

In an important post hoc analysis, Kandzari et al. (4) reported "dose-response" findings with radiofrequency ablation suggesting that inadequate denervation was a root cause of the trial's failure. In this publication, one can see a substantial "dose response" in blood pressure lowering as a function of the number of ablations performed per patient (4). We believe that the SYMPLICITY HTN-3 trial was flawed and should be interpreted not as a global failure of RDN but primarily as a failure to denervate.

In the aftermath of this trial, there has been extensive analysis of the inherent strengths and limitations of the different types of technologies used to perform RDN. It is evident that a successful denervation device must provide predictable, deep, and circumferential nerve inactivation. This is being taken into consideration with current trials of radiofrequency ablation, which are targeting distal ablation in the renal arteries, ablation in the distal branch vessels, and a substantially greater number of thermal ablations than were performed in the SYMPLICITY HTN-3 study. Alternatively, chemical RDN with alcohol, as performed by the Peregrine Catheter (1), may overcome the limitations of radiofrequency-mediated RDN.

In conclusion, much has been learned since the failure of SYMPLICITY HTN-3 about the pathophysiology of RDN. Anatomic, technical, and procedural variables, as well trial execution, must be carefully considered when evaluating RDN clinical trials. We remain optimistic that the refinements in technology will demonstrate the value of RDN for the treatment of difficult to control hypertension, as well as other cardiovascular disorders.

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Please note: Dr. Fischell is a cofounder of Ablative Solutions, has equity, and is a paid employee of Ablative Solutions.

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The Role of Valve Implantation Height

Are We Measuring Depth the Right Way?

We read with great interest the paper by De Torres-Alba (1) on changes in the rate of pacemaker implantation after transition from the SAPIEN XT to the SAPIEN S3 transcatheter aortic valve (Edwards Lifesciences, Irvine, California). The investigators showed, in agreement with other reports, that the rate of pacemaker implantation is almost double with the SAPIEN S3 valve and that depth of implantation is associated with increased rate of permanent pacemaker placement (2–4).

We agree that the deeper the implantation of any device, the higher the risk for complete heart block and need for a pacemaker, given the proximity to the conduction system. This phenomenon seems to be more common with the S3 device, either because of its longer frame or because of its bulkier skirt. However, the accuracy and the magnitude of the association between depth and conduction disturbances as reported are debatable given the methods that were used for depth measurement.

Indeed, there may be flaws in the way implantation depth was estimated before prosthesis deployment and flaws in the way depth was measured after prosthesis deployment. As the investigators describe, 2 angiographic still frames were used to measure implantation depth: 1 pre- and 1 post-implantation. Before the prosthesis is deployed, the aortic annulus is seen in a coaxial projection, with the 3 cusps aligned. This projection is determined either by multislice computed tomography before the procedure or by aortography. The device is then positioned in the annulus, and once the desired depth is achieved, the device is deployed. After deployment, the device is not necessarily coaxial, so the projection is modified to obtain device coaxiality, and this is when final aortography is performed and depth is measured. In this modified projection, however, the aortic annulus is no longer coaxial. Proper localization of the hinge point between the device and sinus