

TRANSLATIONAL PERSPECTIVES

Commentary: Renal Nerve Denervation Is Renervation an Issue?



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Although pharmacological antihypertensive therapy effectively controls blood pressure (BP) in over 90% of patients with hypertension, there is an unmet need for a large segment of the population who are at risk. The body of evidence linking enhanced sympathetic nerve activation as a significant contributor to higher BP makes renal denervation (RDN) an alternative target.

Catheter-based RDN has been shown to significantly reduce BP in the SYMPPLICITY HTN-1 and SYMPPLICITY HTN-2 trials, also demonstrating the safety of the procedure. As stated by Tellez et al. (1), SYMPPLICITY HTN-3—the first prospective, sham-controlled, randomized, double-blinded RDN study—failed to meet its primary or secondary efficacy points. Many possible explanations for the disappointing results have been put forth. The publication of SYMPPLICITY HTN-3 effectively halted most ongoing studies and research in the field. Of all likely explanations, the largest criticisms relate to the misunderstanding of renal nerve anatomy and sub-optimal catheter design. This was compounded by inadequate operator technique and experience.

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The perspective by Tellez et al. (1) in this issue of *JACC: Basic to Translational Science* timely summarized the current status of the RDN therapy. One of their hypotheses is that the best surrogate for RDN, that is, the reduction of post-procedure renal norepinephrine (NE) levels, is not sensitive enough to judge success. A possible counter argument and a more pragmatic approach to measuring NE levels has been suggested. Gal et al. (2) performed a human trial where several patients underwent a pulse of high-frequency renal nerve stimulation before and after

the RDN. It was observed that all blunted hypertensive response to the nerve stimulation was a meaningful and practical way to test the success of the procedure.

Tellez et al. (1) discuss in detail the effect of “neuromatous regeneration” as an important reason for the failure of treatment despite delivering optimal therapy. As supportive evidence is the publication from Prochnau et al. (3), in which a decrease in office BP was noted only when an initial radiofrequency RDN in 10 “nonresponder” patients was followed by a second procedure, in this case renal artery cryoablation.

Against their claim, however, is significant evidence from the RDN Global Registry with over 1,000 patients treated mostly with a monoelectrode catheter. In 75% of the subjects, at 1 year post-procedure, both office and 24-h BP continued to drop (4). Likewise, others using newer-generation, multielectrode catheters have found ongoing lower BP readings up to 24 months following RDN. Although an argument can be made about possible renervation, at the present time there is no evidence that regenerated nerve fibers will reactivate a significant sympathetic output.

Recent and comprehensive animal studies may show the way toward future human trials. Mahfoud et al. (5) examined the effect of different patterns of lesion placement in swine. In their experiments, performed at a single time, RDN efficacy and consistency was determined by a drop in renal tissue NE and decreased renal axon density. The investigators used the multielectrode Spyrax catheter (Medtronic, Minneapolis, Minnesota) that delivered 4 thermal injuries at a time to the main renal artery and its branches. This technique was highly effective in ablating the biochemical and anatomical surrogates of

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sympathetic nerves. A double thermal injury to the main renal artery failed to bring any further inhibition.

The disappointing results of SYMPPLICITY HTN-3 relate to lack of response to the initial RDN, not to a gradual return to higher BPs, as Tellez et al. (1) imply. With a new generation of radiofrequency and ultrasound devices, RDN needs to be a simplified, angiographic event. A secondary procedure would be difficult to accept and increasingly onerous. Also, if correct, the assumption by Tellez et al. (1) would require any subsequent RDN to be applied at the precise site where the initial thermal injury occurred. There is no current imaging, biochemical, or functional testing that could identify unequivocally the site of a previous thermal injury, thus making their hypothesis theoretical and impractical.

In summary, the perspective by Tellez et al. (1) adds to the notion that renal renavation could be another contributor to the failure of RDN. It is far more likely that lack of understanding of the anatomy of renal nerves and less effective first-generation devices, coupled with poor technique and poor patient selection, were the culprits for the negative results of SYMPPLICITY HTN-3.

Should renavation ever become an issue, such as in patients where initial success is followed by an increase in BP, future research should focus on ways to identify the site of a previous injury.

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