Patients with resistant hypertension continue to pose a therapeutic challenge to physicians. These patients often do not achieve the recommended targets for systolic and diastolic blood pressure despite treatment with multiple drugs with an array of mechanisms. In many cases, patients are intolerant or are not compliant, and some of these drugs lack adequate efficacy and are costly. These issues motivated inventors to revive an old concept of surgical sympathectomy, which was used in 1950 and was abandoned due to the morbidities associated with the procedure and availability of new drugs. The novel idea was to use a minimalistic invasive approach for sympathetic denervation with catheter-based radiofrequency modulation delivered to the renal arteries (1). The hypothesis was that destroying sympathetic nerves along the arterial wall of the renal arteries using radiofrequency energy would result in significantly reduced blood pressure in patients with resistant hypertension. The initial feasibility trials performed in patients with resistant hypertension were encouraging and resulted in significant reduction of office blood pressure. Further physiological studies demonstrated a reduction in the norepinephrine spill and muscle sympathetic nerve activity after the radiofrequency modulation, and these findings were correlated with reduced blood pressure (2). The early feasibility studies also demonstrated the durability of the effect and safety profiles of the technology (3).

Subsequently, a small, randomized, open-label trial, SYMPLICITY HTN-2 (Renal Denervation in Patients With Uncontrolled Hypertension), with 106 patients was conducted and confirmed the results of the early feasibility studies (4). As a result, the field exploded with the development of multiple approaches to destroy the renal artery sympathetic nerves. These systems used differently designed catheters to deliver an array of energies, such as radiofrequency, ultrasound, and ionizing radiation—internally or externally (5). Another approach was to apply chemical denervation with local delivery of neurotoxic drugs to destroy the renal artery sympathetic nerves. Among the chemical denervation systems is the Peregrine System, which uses microdoses of alcohol via a proprietary local delivery catheter (6). The evolution of the field included multiple small, nonrandomized feasibility studies in patients with resistant hypertension using many of these novel systems. Nearly all of them reported impressive efficacy in the reduction of the office-based systolic and diastolic blood pressure, with a modest reduction in the ambulatory blood pressure. Surprisingly, the reduction in the blood pressure at 30 days and post-treatment was similar across all studies irrespective of the system and the methodology used. The same now applies to the Peregrine System, and in this issue of JACC: Cardiovascular Interventions, Fischell et al. (7) report a significant reduction in the office-based systolic blood pressure by 24 mm Hg and an average reduction in antihypertensive medications from 3.4 (baseline) to 2.0 per subject at 6 months (8).
the conducting of the small feasibility studies, the results of the pivotal SYMPLICITY HTN-3 study were published (9,10). The SYMPLICITY HTN-3 was a well-designed randomized study that included sham control conducted in 535 patients. Although the study met its primary safety endpoint, it failed to demonstrate efficacy in reducing blood pressure when compared with the control. The lack of efficacy posed a question regarding the validity of the early feasibility results and the future of destroying renal sympathetic nerves as an effective means to control resistant hypertension. Researchers have postulated many theories and hypotheses to explain the disappointing results of SYMPLICITY HTN-3. Among those results are deficiencies related to the radiofrequency system used in the study, operator-related issues, lack of ablation, insufficient circumferential ablation, and not being distal enough (9). Data from autopsies suggested that the target for ablation should be in the distal renal arteries, where there is a high density of the sympathetic nerve, and the importance to ablate circumferentially in the renal arteries (11).

If these are the main reasons for the failure of the efficacy of SYMPLICITY HTN-3, chemical denervation can resolve these issues as the alcohol can be spread diffusely, circumferentially, deeply, and distally and has the potential to affect more sympathetic nerves via the chemical approach. The downside is the lack of control and selectivity of the alcohol to the nerves and the risk that alcohol may potentially damage adjacent tissue. Therefore, it is comforting to learn about the safety profile of the Peregrine System from the preclinical trials and from the feasibility study, although limited to 6 months angiographic and clinical follow-up. These findings positioned the chemical ablation as a safe, simplistic approach with the potential to achieve the goals of effective denervation. However, there are other explanations for the failure of the efficacy in the SYMPYLCITY HTN-3 trial, which are not technology dependent. These are related to patient selection, especially those with resistant hypertension without differentiation to the causality of the patients being resistant to the medical therapy, variability in the overall sympathetic activity of patients who are enrolling into the trials knowing that the sympathetic nerve system is not limited to the renal arteries, and possible compensation to the renal sympathetic denervation by other sympathetic nerves outside of the renal arteries. Further, the mechanism for hypertension is multifactorial and not necessarily dominated by the sympathetic system, especially in elderly patients who experience stiff, non-compliant atherosclerotic arteries. While renal sympathetic nerve ablation has some effect on blood pressure, it may be naïve to believe that ablation of the renal sympathetic nerves alone will be sufficient to control resistant hypertension. Finally, there are other study-related issues with respect to the study population—the change in medications during the trial and the lack of immediate metrics to ensure that effective ablation was obtained either by mapping or immediate drop in blood pressure similar to the methodologies that are used in the electrophysiology field. Perhaps the main contribution of the SYMPLICITY HTN-3 trial is that it resulted in a consensus that we need large randomized clinical trials with a sham control to assess the efficacy of the technology. Meanwhile, it is imperative to understand the reasons for the failure of efficacy in the SYMPLICITY HTN-3 study. If the failures are not technology related and more driven by disease heterogeneity and variability in response, we should not expect a change in the results when chemical denervation, or any other technology, is tested in a large randomized clinical trial.

There are several deficiencies with the clinical trial performed by Fischell et al. (7), making it challenging to draw definitive conclusions on efficacy and the safety of the technology. The number of patients in the study was small, and the follow-up was limited to 6 months. Ambulatory blood pressure monitoring was not available at the trial site and was not included in this study protocol; there was no independent clinical event committee to adjudicate the events; and the principal investigator participated in the adjudication of the events. The investigators have chosen only 1 dose for the study. In the future, it would be interesting to examine how higher or lower doses affect and optimize the safety and efficacy profile of this system. Finally, it is unusual that the American company and investigators selected to perform their investigation in Paraguay. Such early feasibility studies should be conducted in the United States under the early feasibility studies program, which has been initiated by the U.S. Food and Drug Administration. This would add to the transparency and the integrity of the study and facilitate a smooth transition for a pivotal study in the United States.

Clearly the field of renal denervation is not that simple, but chemical renal denervation is a simplistic method to perform renal denervation. It is feasible and perhaps safe, but to prove efficacy, researchers would have to address a rather complex, challenging field in a large randomized trial. Meanwhile, it would be wise to await the results of 2 pilot studies using second-generation radiofrequency technology with a novel study design, including moderate
hypertension. The SPYRAL HTN-OFF MED and REDUCE-HTN: REINFORCE (Renal Denervation Using the Vessix Renal Denervation System for the Treatment of Hypertension) studies are currently enrolling and implementing the lessons from the SYMPLICITY HTN-3. The results of these 2 studies will have a major role in directing the future of renal denervation. Patients, physicians, and industry should look forward to this important milestone.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Ron Waksman, 110 Irving Street NW, Suite 4B-1, Washington, DC 20010. E-mail: ron.waksman@medstar.net.

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