

EDITORIAL COMMENT

# Renal Sympathetic Denervation for the Treatment of Ventricular Arrhythmias



## A Lesson in Not Throwing Out the Baby With the Bathwater?\*

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*Just because something doesn't do what you planned it to do doesn't mean it's useless.*

-Thomas Edison (1)

Cardiac catheter ablation of scar-related ventricular tachycardia (VT) is safe and effective for reducing recurrent VT episodes and implantable cardioverter-defibrillator (ICD) therapies (2). Nevertheless, even in high-volume centers with skilled operators, between one-third and one-half of patients will have a recurrence of sustained ventricular arrhythmias (VAs) within 1 year after catheter ablation for scar VT (2,3). Predictors of VA recurrence after ablation include nonischemic substrate, heart failure class, unstable/unmappable VTs, persistent inducibility at the end of the procedure, and presentation with VT storm (4). Because failure to control recurrent VAs is associated with a higher risk of subsequent death, there has been intense interest in the development of adjunctive therapies to further suppress VAs in patients not adequately controlled with pharmacological and conventional catheter ablation procedures (5).

To this point, the sympathetic nervous system has long been implicated in the initiation and perpetuation of VAs (6-8). Most recently, nonrandomized studies have suggested that either thoracic epidural anesthesia or left/bilateral stellate gangliectomy, a minimally invasive surgical procedure, can modulate

the sympathetic nervous system and significantly reduce recurrent VAs in patients in whom conventional therapies fail (9,10). Not surprisingly, investigators have turned their eye toward even "simpler" methods for modulating the autonomic nervous system—catheter ablation of the sympathetic nerve fibers coursing in the renal arterial adventitia (renal sympathetic denervation [RSDN]). Although the Symplicity HTN-3 (Renal Denervation in Patients With Uncontrolled Hypertension) trial did not demonstrate a benefit of RSDN (compared with placebo) for the treatment of resistant essential hypertension, RSDN has been shown to modify measures of sympathetic overactivity, such as renal/whole-body norepinephrine spillover and muscle sympathetic nerve activity (11,12). Furthermore, pre-clinical data have demonstrated that RSDN can suppress VAs during acute ischemia, and case reports of patients with either recurrent VAs after catheter ablation or who presented with electrical storm suggests that RSDN may be beneficial (13-16). However, it should be noted that the total published clinical experience numbers only 6 patients from 5 institutions and did not account for confounding variables (e.g., upgrade to cardiac resynchronization therapy, titration of antiarrhythmic therapies), which could have overestimated the perceived effect of RSDN.

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In this issue of the *Journal*, Armaganijan et al. (17) shed additional light on the important clinical question of whether catheter-based RSDN has the potential to reduce recurrent VAs in patients with cardiomyopathy. In this single-center prospective study, the authors analyzed the 6-month outcomes of 10 patients undergoing RSDN for refractory VAs. The inclusion criteria were VAs refractory to optimal medical therapy

with either previous failed cardiac ablation ( $n = 2$ ) or poor unsuitability for cardiac ablation due to the presence of cardiac thrombus ( $n = 3$ ) or presentation with polymorphic VT or ventricular fibrillation ( $n = 5$ ). More than one-half the patients' VT substrate was due to Chagas disease ( $n = 6$ ). The overall mean left ventricular ejection fraction was  $31 \pm 11\%$ , and patients were taking an average of 2 antiarrhythmic medications on presentation. RSDN was performed with 1 of 2 different catheters: an off-the-shelf irrigated ablation catheter ( $n = 7$ ) (Therapy Cool Path, St. Jude Medical, St. Paul, Minnesota) with which a minimum of 4 ablations per renal artery were delivered (18), or a dedicated RSDN catheter ( $n = 3$ ) (EnligHTN, St. Jude Medical) with which a minimum of 8 ablation lesions per renal artery were delivered. All ICDs were programmed between 120 and 130 beats/min after RSDN. The authors report only 1 significant procedure-related adverse event: bradycardia requiring transient intravenous epinephrine to correct. There were no vascular or renal complications, including the absence of either renal artery dissection or renal artery stenosis (at 6 months of follow-up). Three patients died before completing 6 months of follow-up: 2 died of progressive heart failure and 1 died of sepsis. In total, 7 patients completed the 6 months of follow-up. When comparing the 6 months before RSDN to the 6 months after RSDN, there was a dramatic reduction in VAs and ICD therapies: the median number of VT/VF episodes decreased from 28.5 (range, 1 to 106) to 0 (range, 0 to 9), antitachycardiac pacing therapy decreased from 20.5 (range, 0 to 52) to 0 (range, 0 to 7), and the number of ICD shocks decreased from 8 (range, 0 to 88) to 0 (range, 0 to 3). Although the majority (80%) of patients were considered RSDN responders, 2 patients appeared to derive no discernible benefit (i.e., no significant reduction in VA burden) from the procedure. Importantly, the authors report that no patients required an increase in antiarrhythmic therapy.

The authors have demonstrated that RSDN is feasible and (likely) safe in patients with scar-related VAs, without any deleterious effects on blood pressure or renal function. Furthermore, RSDN, in conjunction with antiarrhythmic therapy, may

dramatically reduce the VA burden in patients with mixed substrates who are not considered candidates for catheter ablation. The strengths of this study include prospective enrollment and data collection as well as a prescriptive approach to defibrillator programming for the detection of VAs. However, enthusiasm for RSDN in the treatment of VAs has to be weighed against the realization that: 1) although this series represents the largest published experience to date, it is still a small number of patients ( $n = 10$ ); 2) heart failure optimization, hospitalization, and anesthesia can potentially affect VA burden and sympathetic tone; 3) RSDN was performed for patients who were not candidates for catheter ablation, so its role as adjunctive therapy remains unknown; 4) measures of sympathetic tone/function were not performed, so one cannot know whether sympathetic tone was actually modified with RSDN (19). Thus, the study by Armaganjian et al. is an important step toward our understanding of the potential role of catheter-based RSDN for the control of scar-related VAs, but studies of RSDN in essential hypertension have taught us not to pop the champagne corks just yet. However, it is interesting to speculate that patients with VAs might represent a population that, because of their highly overactive sympathetic state, may benefit greatly from a therapy like RSDN. As indicated on the clinical trials registration site, this hypothesis is being tested prospectively in a several such randomized clinical trials (NCT01747837, NCT01858194, NCT02071511). Furthermore, in addition to VAs, RSDN is also being explored as an adjunctive treatment for atrial fibrillation, another arrhythmia with autonomic overactivity (20,21). Ultimately, well-designed prospective, randomized clinical trials with appropriate patient blinding are needed to determine whether the beneficial antisympathetic effects of RSDN may prove effective in the control of cardiac arrhythmias.

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