

## Renal Denervation Therapy for the Treatment of Arrhythmias: Is the Sky the Limit?

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As the life expectancy of the general population continues to increase, cardiovascular disease is becoming an increasingly important driver of morbidity and mortality. Many of the recent advancements in our treatment armamentarium against cardiovascular disease center around curbing maladaptive responses to stress. Specifically, neurohormonal modulatory medications are the cornerstones of therapy in patients who suffer myocardial infarction and/or develop systolic heart failure. In such patients compensatory mechanisms become drivers of cardiac pathology.<sup>1</sup> Autonomic dysregulation leads to excessive sympathetic drive, which in turn causes blunted natriuresis and hypertension.<sup>2</sup> Medications such as  $\beta$ -blockers, ACE inhibitors, and aldosterone inhibitors<sup>3-6</sup> help to mitigate adverse neurohormonal changes and improve outcomes in patients with heart failure. Furthermore, medications that interrupt the renin-angiotensin-aldosterone system have been shown to have antifibrotic properties in animal models, as they appear to reduce cardiac fibroblast proliferation and collagen deposition.<sup>7</sup>

Optimizing a medication regimen remains the cornerstone of heart failure therapy, but new invasive catheter-based techniques are being developed and investigated as disease-modifying tools in heart failure. As an example, catheter-based renal denervation (RDN) was conceived as a rational therapy for patients with resistant hypertension.<sup>8,9</sup> Subsequently, this technology was brought to bear on other types of patients in whom modulation of cardiorenal interplay was hypothesized to be beneficial. Of late, there has been

increasing interest in using RDN for the treatment and prevention of arrhythmias and arrhythmia-related morbidity. Animal studies have shown promise. In a canine model of tachycardia-mediated cardiomyopathy, RDN was shown to attenuate ventricular remodeling in animals that are chronically paced at a high rate.<sup>10</sup> In a pig model of myocardial infarction, investigators subjected the animals to myocardial ischemia using 20 minutes of LAD occlusion. Half of the pigs had had RDN, and half underwent a sham procedure. RDN significantly decreased occurrence of ventricular fibrillation during occlusion.<sup>11</sup> There is a paucity of detailed human research on the subject, but some small studies have suggested that RDN could be an effective adjunct to catheter ablation for atrial fibrillation (AF). Pokushalov and colleagues randomized 27 patients with refractory AF and resistant hypertension to pulmonary vein isolation alone vs pulmonary vein isolation plus catheter-based RDN; they found significantly improved arrhythmia control in the RDN arm at 1-year of follow-up.<sup>12</sup>

Two articles published in this issue of *JAHA* explore the pathophysiologic role of renal nerve activity in cardiovascular disease progression in animal models, with a focus on arrhythmia. They serve as forward steps toward expanding the indication for RDN to be used as adjunct therapy for the suppression of AF and the prevention/treatment of premature ventricular contraction (PVC)-mediated cardiomyopathy.

These articles approach the issue from opposite angles. Yamada and colleagues examine whether RDN can prevent PVC-mediated cardiomyopathy.<sup>13</sup> Yu and colleagues attempt to deconstruct the observations from prior animal and human studies that RDN could decrease the incidence of AF; they examine the mechanisms by which renal sympathetic nerve stimulation affects the threshold for the induction of atrial fibrillation.<sup>14</sup>

Yamada et al studied 18 rabbits—6 controls, 6 with a 50% PVC burden, and 6 with a 50% PVC burden plus RDN. The PVCs were generated through epicardial left ventricular apical pacing; RDN surgery involved cutting of visible nerves at the renal hilus (bilaterally) along with adventitial stripping of the renal artery. The controls had sham procedures performed for pacing and RDN. The animals were followed for 5 weeks, at which point they underwent echocardiography,

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electrophysiology study, and pathologic analysis of harvested myocardium. Yamada et al found that the rabbits with high PVC burden without RDN developed left ventricular enlargement and biventricular fibrosis. Additionally, these animals were more readily induced into ventricular fibrillation during programmed ventricular stimulation. Importantly, the animals with PVCs plus RDN fared comparably to the controls.<sup>13</sup>

Yu et al studied 28 dogs and sutured electrode catheters to their renal arteries. They then performed 3 hours of high-frequency stimulation at the proximal, mid, and distal portions of the renal artery. With renal nerve stimulation, they observed a hypertensive response, shortening of the effective refractory period at a number of atrial sites, and a widening of the window of vulnerability for AF induction. Importantly, the authors demonstrate that the proximal portion of the renal artery appears to be the most important in cardiorenal interplay; stimulation at this proximal portion of the renal artery produced the greatest hemodynamic effect and the most pronounced shortening of atrial refractory periods. C-fos and NGF gene and protein expression as well as left stellate ganglion activity and superior left ganglionic plexus activity were also measured in response to renal nerve stimulation. The authors note upregulation and increased activity of all of the above and make the claim that left stellate ganglion and superior left ganglionic plexus activation is the mechanism by which renal nerve stimulation “exerts pro-fibrillatory effects on the atrium.”<sup>14</sup> This conclusion is not well substantiated, as no causative relationship can be drawn from the data provided. Ultimately, the authors are left describing phenomenology and not a true biochemical blueprint for how renal nerve stimulation modulates atrial electrophysiologic properties.

The studies by Yamada and Yu represent small but important incremental steps in defining the role of renal afferents in modulating the cardiac electrical milieu and in serving as a key link in the pathologic cardiac response to hemodynamic stress. The documented effects of renal nerve activation/inhibition on both arrhythmogenesis and ventricular dysfunction speak to the close link between kidney and heart.

Although these studies are intriguing, they are clearly only hypothesis generating, as they employ animal models, small sample sizes, and limited monitoring time frames. The mechanisms by which renal nerve manipulations affect arrhythmogenesis are, as yet, incompletely elucidated. Future directions for investigation should include follow-up animal studies first—for instance, it would be of great interest to allow subjects to develop a PVC-mediated cardiomyopathy prior to performing RDN; an examination of whether RDN is capable of fostering reverse ventricular remodeling would be informative for the practical scope of this modality. Likewise, a before-and-after RDN study of AF inducibility would be

useful because allowing each animal to be its own control may allow for more credible conclusions.

Eventually, it is conceivable that RDN could be used in humans both to prevent arrhythmia (atrial and ventricular) and also to treat the adverse sequelae of arrhythmia (ie, tachycardia-mediated cardiomyopathy in AF, heart failure with preserved ejection fraction in AF, and PVC-mediated cardiomyopathy). Clinical scenarios in which RDN might be used are myriad; these include the prevention/treatment of cardiomyopathies associated with PVCs that are not suppressed with antiarrhythmic drugs and not amenable to catheter ablation, as a same-procedure adjunct to AF ablation, and as a treatment for ventricular storm and other ventricular tachyarrhythmias refractory to conventional therapies. Renal denervation might also be useful for niche indications such as a less invasive alternative to thoracoscopic sympathectomy in patients with long-QT syndrome. As with all new invasive interventions, careful patient selection and refining and standardization of procedural techniques are paramount.

When considering new invasive therapeutic interventions, it is important to be mindful of the potential damage that can result. Catheter-based approaches for RDN are inherently associated with a risk of vascular complications.<sup>15</sup> As always, the unintended consequences of manipulating the body’s adaptive mechanisms may not become clear until a given therapy is applied in a substantial number of people (with long periods of follow-up). Last, any future trials of RDN therapy must be designed with robust sham procedure arms. As was shown by the SYMPPLICITY HTN3 investigators, the influence of a sham placebo is powerful—in examining the blood pressure benefit of bilateral catheter-based RDN, they found (to everyone’s surprise) no significant antihypertensive effect of RDN.<sup>16,17</sup> With the above caveats in mind, the future looks bright for the use of RDN in arrhythmia control.

## Disclosures

None.

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