The Multipotential of Renal Denervation: To Treat Hypertension and Beyond

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Abstract

Renal denervation is a catheter-based procedure to modulate sympathetic output to kidneys to treat refractory hypertension, reduce ventricular arrhythmia, lower atrial fibrillation burden, and improve aortic stiffness and symptoms of heart failure with preserved ejection fraction. The industry-led approach utilizes customized catheters to target both renal arteries without a clear procedure endpoint and has failed to demonstrate consistent results in treating hypertension. However, this catheter-based intervention to modulate sympatho-excitation remains attractive for clinicians to target a variety of diseases. High-frequency stimulation-guided renal denervation uses a conventional ablation catheter and a three-dimensional mapping system and has shed some light on extinguishing refractory ventricular arrhythmias, reducing the recurrence of atrial fibrillation, and providing new therapy for heart failure with cardiorenal syndrome.

Keywords: renal denervation, sympathetic modulation, ventricular arrhythmias, atrial fibrillation, hypertension, heart failure

Introduction

Renal denervation (RDN) is a catheter-based procedure utilizing radiofrequency to destroy the nerve surrounding the renal vasculature. RDN was initially conceived as a procedure to overcome diuretic resistance in heart failure (HF). However, the first-in-human study in 2007 demonstrated a greater than expected effect in lowering arterial blood pressure (BP), initiating a broad exploration of RDN's antihypertensive effect.[1] The most common indication for RDN is now resistant hypertension (HTN), however, emerging evidence is showing that the neuromodulating effect of RDN has therapeutic potential extending beyond HTN into arrhythmias and heart failure. This review critically examines the current evidence from bench to bedside and provides future direction.

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Conflicting results of RDN in hypertension

Renal afferent and efferent nerves are known to play an important role in renal function and BP control, based on evidence of increased renal sympathetic nerve activity in hypertensive humans.[2] Earlier non-randomized studies have shown that surgical sympathectomy can effectively treat uncontrolled hypertension, but profound orthostasis develops afterward.[3] The development of the catheter-based RDN technique has revived interest in this procedure. However, the efficacy remains debatable. The initial non-randomized Simplicity HTN-1 trial followed 88 patients for up to 3 years and found 93% of them to have an office BP that was 10mmHg lower than the baseline.[4] Similarly, the randomized and unblinded Simplicity-HTN2 trial demonstrated a 28 mmHg office BP decrease after 6 months in 47 patients.[5] However, Simplicity HTN-3, the first randomized sham-controlled trial, failed to demonstrate 24-hour ambulatory BP reduction, compared with the sham group.[6] The latest two randomized sham-controlled trials, SPYRAL HTN ON-MED and SPYRAL HTN OFF-MED, utilizing second-generation techniques and targeting the distal renal artery and its branches, showed significant, consistent 24-hour ambulatory BP-lowering effects near 10 mmHg.[7,8]

One proposed mechanism for the neutral result of Simplicity HTN-3 is functional and anatomical re-innervation. It was reported that after surgical renal RDN in rats, there is immunohistochemical evidence of functional and anatomical re-innervation within 12 weeks and 8 weeks.[9,10] Taking into account the differences in body size and technique, studies of porcine models with Symplicity and alternative catheters were conducted. These porcine models support the efficacy of RDN with evidence of reductions in renal norepinephrine, cortical axon density, and downstream axonal loss through 180 days post-RDN.[11] This result, however, is not consistent with other studies using sheep models. Booth et al. first utilized electric nerve stimulation and confirmed the efficacy of denervation immediately after RDN and found that after 5.5 months, reinnervation was almost complete.[12]

Physiologically, it is conceivable that reinnervation is inevitable given the fact that soma is not damaged during a standard RDN procedure. In total, given the conflicting results from clinical and animal studies, the myriad factors involved highlight the necessity of developing a novel approach towards RDN.

RDN as an adjuvant therapy for refractory ventricular arrhythmias

Ventricular arrhythmias (VAs) are life-threatening arrhythmias and implantable cardioverter defibrillators (ICDs) are the mainstay of treatment.[13] It should be noted that ICDs are life-saving devices, but recurrent ICD shocks lead to increased risk of heart failure, mortality and significantly impaired quality of life.[14] The rapidly evolving knowledge and techniques for catheter ablation for VAs have shown it to be an effective treatment for drug-refractory VA, in terms of freedom from VA and the possibility of lowering mortality when performed in time.[15,16] Despite the improvement of catheter ablation, acute procedural success is reported to be only 56% to 77% in patients with ischemic cardiomyopathy and 38% to 67% in patients with non-ischemic cardiomyopathy. In the long-term, 30% to 50% of patients suffer recurring symptoms.[17]

The sympathetic system plays a critical role in the initiation and maintenance of VAs, with mechanisms involving heterogeneity of innervation, hypersensitivity to circulating catecholamines, alteration of the action potential duration restitution curve, and enhanced automaticity.[18] It has been shown in the ischemic porcine model that RDN attenuates VA occurrence.[19] Clinically, the efficacy of RDN attenuating VAs has only been explored in small-scale studies, owing to the scarcity of patients.[20] Seven updated studies demonstrated high efficacy in reducing VA burden and terminating electrical

storms in both ischemic and non-ischemic VAs. Importantly, only one paper by Bradfield et al. included patients with prior cardiac sympathetic denervation, suggesting the additive anti-arrhythmic effect of RDN.[21] Among these studies, Kiuchi et al. performed RDN in patients with chronic kidney disease, guided by high frequency stimulation instead of the conventional Symplicity system. They showed that RDN reduced VT burden, especially in chronic kidney disease stages 3 and 4.[22] Although RDN appears to be a safe and effective treatment for refractory VAs, studies based on randomized data are necessary to evaluate the effect.

RDN reduces atrial fibrillation burden in patients with hypertension

Atrial fibrillation (AF) is the most common sustained arrhythmia worldwide, with significant effects on cardiovascular-related morbidity and mortality.[23] Hypertension, as a well-known risk factor for AF, is associated with an increased sympathetic tone. Studies have reported that increases in sympathetic tone are observed in humans prior to the onset of AF.[24] Accumulated evidence has shown that pulmonary vein isolation is recommended in patients with symptomatic paroxysmal or persistent AF refractory to anti-arrhythmic medications.[23] The long-term recurrence rates, however, with pulmonary vein isolation alone, remain suboptimal, especially in persistent AF. Several strategies have been investigated to find a possible solution, including substrate modification (STAR AF II),[25] posterior wall isolation (CAPLA),[26] and left atrial appendage isolation.[27]

Pokushalov et al. first reported a significant AF reduction, including in persistent AF, and significant recurrence reduction, in patients with severe resistant hypertension after RDN guided by high-frequency stimulation with the CARTO mapping system (Biosense-Webster, Diamond Bar, CA).[28] Recently, a larger RCT, the Evaluate Renal Denervation in Addition to Catheter Ablation to Eliminate Atrial Fibrillation (ERADICATE-AF) trial, also reported that adding RDN to conventional PVI significantly decreases the recurrence rate of AF in patients with hypertension and paroxysmal AF.[29] Notably, intensified peri-ablational antihypertensive medications fail to improve postprocedural outcomes,[30] highlighting the mechanism by which RDN mediated AF outcome may involve better BP control and sympatholysis. There are, however, conflicting results showing that RDN with pulmonary vein isolation does not reduce AF in patients with chronic kidney disease, stages 2 or 3. The results emphasize how little we know about the nuances of vagal-sympathetic imbalance in initiating and maintaining AF. Adrenergic AF usually terminates spontaneously, while vagal AF tends to be maintained, based on the evidence that, after sympathetic stimulation, the spiral waves tend to organize and terminate immediately, whereas, after parasympathetic stimulation, the spiral wave reentries show a tendency to linger due to the prolonged refractory period.[31] Therefore, it is conceivable that RDN can only partially modulate the autonomic component in this complex arrhythmia.

RDN as a novel therapy for heart failure and cardiorenal syndrome

Despite the progress in treatment for heart failure with reduced ejection fraction, heart failure with preserved ejection fraction (HFpEF) remains a major challenge.[32] The interaction between hypertension, vascular stiffness and sympatho-excitation contributes to the conundrum of HFpEF.[33] Evidence has shown that RDN reduces aortic stiffness and sympatho-excitation, and thereby improves diastolic function.[34,35] To date, there has been only one randomized study, the Renal denervation in heart failure with preserved ejection fraction (RDT-PEF) study, but it had to be terminated prematurely because of difficulty in recruitment, leaving it underpowered.[36] Later Kresoja et al. presented the best evidence so far

for RDN in HFpEF. The authors investigated hemodynamic and physiological changes in detail in patients with and without HFpEF who underwent RDN for hypertension at their center. It should be noted that 99 patients (60%) met the criteria for hypertension plus HFpEF, highlighting how HFpEF often presents under the guise of hypertension. They showed that RDN has positive hemodynamic effects on cardiac and vascular performance and thereby improves symptoms of HFpEF, independent of the changes in BP. This encouraging finding underscores the inadequacy of identifying BP as a solitary marker of technical success and the important role of sympatho-excitation in HFpEF.[37]

The cardio-renal syndrome (CRS) type 2, defined as a progressive loss of renal function after a primary cardiac insult, is a difficult disease to treat which often progresses to end-stage renal disease when conventional therapy fails.[38] The kidneys communicate with the central nervous system via the renal sensory afferent nerves, based on evidence that renal insults such as ischemia or hypoxia could elicit afferent renal nerve responses.[39] RDN is likely to be a potential treatment for CRS, based on the observation that the afferent signals directly influence sympathetic outflow to the kidneys, the heart and peripheral blood vessels, which are also modulated by the paraventricular nucleus.[40] RDN in rodent models with chronic kidney disease has been shown to reduce sympathetic tone, resulting in a decrease in arterial blood pressure. Further selective afferent renal nerve denervation results in attenuation of the exaggerated renal and splanchnic nerve activity, thereby improving the glomerular filtration rate, and attenuating renal fibrosis.[41] The findings were further supported by Chen et al., who demonstrated that RDN in rats with CKD could normalize GABAergic changes in the nucleus tractus solitarius and improve baroreflex function, plasma levels of norepinephrine, glomerulosclerosis, and renal tubular injury.[42] This novel implication warrants large, translational animal studies and, further, clinical studies.

Challenges in RDN- toward better endpoints and potent target

It should be noted that in the studies targeting hypertension led by the industry, specific catheters were used, such as in SIMPLICITY and SPYRAL, while in other studies investigating arrhythmias led by clinicians, conventional mapping/ablation catheters were used. Importantly, in studies using specific catheters, there were no unified target and procedure endpoints. This might account for the heterogeneous result of the failed SIMPLICITY HTN-3 study, in which operators created lesions (3-4tims), compared with the SIMPLICITY HTN-1 and HTN-2 studies. This heterogeneity was not seen in other studies using high-frequency (20 Hz) stimulation to define the target. The investigators also used the elimination of BP change during high-frequency stimulation as the procedure endpoint. This difference between approaches warrants rigorous study to develop an effective approach for RDN.

Recently, the aorticorenal ganglion (ARG) has emerged as an attractive target warranting detailed evaluation. The left ARG is located inferior to the superior mesenteric artery and abuts the posterosuperior aspect of the left renal vein. The right ARG is located between the IVC and the descending aorta, superior to the right renal artery. (Figure 1)[43] The concept of targeting the ARG was initially proposed by Qian et al.[44] In a sheep model, transvascular high-frequency ARG stimulation (10 Hz, 25 mA) induced a hypertensive response and ipsilateral renal artery vasoconstriction. This proof-of-concept was later followed up by Hori et al., showing the superior effectiveness of targeting the ARG, compared to targeting the renal nerves.[45] They demonstrated that the ARG stimulation effect cannot be eliminated by ablating the renal artery nerves but the response could be suppressed by ablating the ARG. Importantly, ARG ablation provides a cardioprotective effect against ischemia-induced VAs, compared with RND. Further studies are required to transition the procedure into humans.

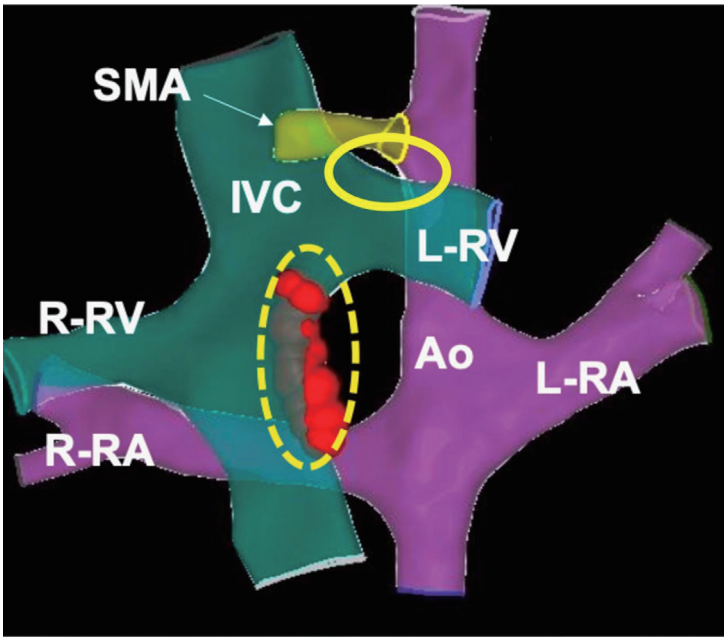

Figure 1. 3-dimensional mapping of aorticorenal ganglion.
Figure 3 illustrates the anatomical relationships between the inferior vena cava (IVC), abdominal aorta, and aorticorenal ganglion (ARG). Note that the right ARG (dashed circle) is located between the IVC and descending aorta, abutting both, and is superior to the right renal artery. The left ARG (solid circle) is located posteriorly to, and abuts, the left renal vein, and is next to the superior mesenteric artery. Ao = aorta; IVC= inferior vena cava; L-RA = left renal artery; L-RV = left renal vein; SMA = superior mesenteric artery. (Figure adapted courtesy of Dr. Taro Temma.)

Conclusions

The complexity of the kidney, heart and sympathetic system contributes to a wide disease spectrum, including hypertension, ventricular arrhythmias, atrial fibrillation, heart failure with preserved ejection fraction and cardiorenal syndrome. Renal denervation has unlocked a new pathway for partially modulating sympatho-excitation based on a catheter procedure. The effect of RDN remains heterogeneous and warrants the development of a better procedure endpoint and a more potent target to refine this attractive intervention.

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