The Effects of Renal Denervation beyond Anti-hypertension

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Abstract

Renal denervation (RDN) disrupts afferent and efferent sympathetic nerves surrounding the renal artery and reduces sympathetic activity. The effects of RDN on uncontrolled hypertension have been well studied in previous clinical trials, and RDN may also have clinical roles in some diseases which are associated with sympathetic nervous overactivity. Early pilot trials revealed RDN had positive effects on atrial fibrillation, heart failure, obstructive sleep apnea, and insulin resistance. This review focuses on the most recent evidence from large-scale randomized controlled trials, non-randomized clinical trials and meta-analyses. Moreover, several small clinical trials have revealed that RDN could also benefit patients with advanced chronic kidney disease, who were excluded from previous studies. In conclusion, the emerging data warrants further investigation into the effect of RDN beyond preventing hypertension.

Keywords: renal denervation, atrial fibrillation, heart failure, sleep apnea, metabolic syndrome

Introduction

Emerging randomized controlled trials are showing the benefits of renal denervation (RDN) in uncontrolled hypertension.[1] RDN disrupts afferent sensory nerves surrounding the renal artery and reduces sympathetic activity. Patients with additional diseases also associated with sympathetic overactivity may also benefit from RDN. Clinical situations other than uncontrolled hypertension have been tested or investigated in published studies, such as metabolic syndrome, obstructive sleep apnea (OSA), atrial fibrillation (AF), ventricular arrhythmia, heart failure, and chronic kidney disease (CKD). Indication beyond hypertension control is expected in new clinical trials because the results of pivotal studies have been positive and also some large-scale, long-term, randomized clinical trials have been published. Table 1 lists the studies regarding RDN in non-hypertensive target populations.

Application in atrial fibrillation

The relationship between the autonomic

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Table 1

	CASE-CONTROL & COHORT	CLINICAL TRIAL	META-ANALYSIS	UNPUBLISHED
ATRIAL FIBRILLATION	RDN adjunctive to PVI prevented AF recurrence[3,4] RDN reduced AF burden and improved QoL.[7]	RDN plus cryoablation reduced AF recurrence (ERADICATE-AF).[8]	RDN adjunctive to PVI prevented AF recurrence.[10]	RDPAF* (NCT01990911) ASAF† (NCT02115100) SYMPLICITY AF (NCT02064764) ULTRA-HFIB‡ (NCT04182620)
HEART FAILURE WITH REDUCED EJECTION FRACTION	RDN reduced ventricular arrhythmia episodes and RDN increased 6-minute walk distance.[12,18]	RDN lowered blood pressure and improved LV function[19] RDN improved diastolic function and reduced LV mass.[17] RDN lowered NT-proBNP and glucose intolerance but not LV function (SYMPLICITY-HF).[24]	RDN improved LV function, 6-minute walk distance, and decreased NT-proBNP.[25] RDN improved LV function and decreased NT-proBNP.[26]	RE-ADAPT-CHF§ (NCT02085668) RSD4CHF? (NCT01790906) REACH# (NCT01639378) NCT01870310 NCT01402726
OBSTRUCTIVE SLEEP APNEA	RDN lowered blood pressure and AHI in OSA.[29-31] No effect on blood pressure in resistant hypertension patients with untreated OSA.[32]	RDN lowered AHI, improved the severity of OSA.[35]	RDN led to lower blood pressure and AHI in OSA, less nocturnal awakenings, and improvement of nocturnal oxygen saturation.[33]	
DIABETES MELLITUS	RDN lowered insulin resistance.[39,40]	Results vary.[41-43]	No significant change after RDN in glucose metabolism.[44]	
CHRONIC KIDNEY DISEASE	RDN was safe in patients with eGFR 15-45 mL/min/1.73 m^2.[46,50,51] RDN improved renal function in patients with stage 2 CKD.[48]	RDN was safe and effective in AF and reduced LV mass with or without CKD.[5,6,49] RDN is safe in renal transplant recipient.[45]		RDN-CKD¶ (NCT04264403)

RDN: renal denervation; PVI: pulmonary vein isolation; AF: atrial fibrillation; CKD: chronic kidney disease; QoL: quality of life; AHI: apnea-hypopnea index; OSA: obstructive sleep apnea; LV: left ventricle

* Renal Sympathetic Denervation Prevents Atrial Fibrillation in Patients with Hypertensive Heart Disease: a Pilot Study (RDPAF)

† Treatment of Atrial Fibrillation in Patients by Pulmonary Vein Isolation in Combination with Renal Denervation or Pulmonary Vein Isolation Only (ASAF)

‡ Ultrasound-Based Renal Sympathetic Denervation as Adjunctive Upstream Therapy during Atrial Fibrillation Ablation (ULTRA-HFIB)

§ Renal Denervation in Patients with Chronic Heart Failure (RE-ADAPT-CHF)

? Renal Sympathetic Denervation for Patients with Chronic Heart Failure (RSD4CHF)

Renal Artery Denervation in Chronic Heart Failure Study (REACH)

¶ Renal Denervation in Chronic Kidney Disease Study (RDN-CKD) nervous system and atrial fibrillation has been well studied. The autonomic nervous system can change atrial automaticity, which may induce or maintain AF.[2] A pilot study enrolling 27 resistant hypertensive patients showed that simultaneous AF ablation and RDN led to more freedom from AF recurrence (69% vs. 29%; p=0.033) at 12 months, compared to AF ablation only.[3] Soon afterward, Kuichi et al. conducted two double-blinded, randomized trials. One non-randomized trial in AF patients with CKD also reduced AF recurrence in the RDN group.[4-6] Subsequently, a total of 20 patients in the AFFORD trial with symptomatic AF and mild hypertension showed RDN improved quality of life along with a reduction of AF burden, as counted by continuous implantable monitoring.[7]

The ERADICATE-AF trial was the 1st large-scale randomized trial, enrolling 302 patients receiving antihypertensive drugs who were referred for AF ablation.[8] All were randomized to undergo AF cryoablation plus either RDN or a sham procedure. Compared with cryoablation alone, the addition of RDN during the same procedure increased the rate of freedom from AF recurrence at one year (72.1% vs. 56.5%; HR 0.57; 95% CI: 0.38-0.85), by which time the number needed to be treated was only six for one year/person. The HFIB trial was a multi-center, double-blinded, randomized controlled trial to investigate the hypothesis that adjunctive RDN with AF ablation will prevent AF recurrence.[9] A meta-analysis enrolled the unpublished HFIB data and six other prior studies in 2021. In the HFIB trial, HFIB-1 and HFIB-2 cohorts enrolled 30 and 50 patients, respectively. Both HFIB-1 and HFIB-2 showed no significant difference in AF recurrence in the RDN and control group. However, pooled analysis combining the HFIB study and six prior studies (a total of 725 patients) showed adjunctive RDN significantly decreased the risk of AF recurrence (risk ratio [RR]: 0.68; 95% confidence interval [CI]: 0.55 to 0.83; p=0.0002), when compared with PVI alone.[10] The effect of RDN adjunctive to PVI ablation reducing the AF recurrence has been well studied, but whether RDN alone can prevent new-onset AF is still unknown. In 2019, an abstract of the RDPAF (Renal Sympathetic Denervation Prevents Atrial Fibrillation in Patients with Hypertensive Heart Disease: A Pilot Study; NCT01990911) was announced. The preliminary 80 resistant hypertensive patients, without a prior diagnosis of AF, showed positive results from RDN at a median follow-up >2 years: lower incidence of new AF (RDN 19% vs. sham 47%; p=0.009) on continuous monitoring as the primary endpoint and less cardiovascular death (RDN 2% vs. sham 16%; p=0.049) as the secondary endpoint. Two large-scale randomized controlled trials are ongoing. The ASAF (Treatment of Atrial Fibrillation in Patients by Pulmonary Vein Isolation in Combination with Renal Denervation or Pulmonary Vein Isolation Only; NCT02115100) is a trial observing 138 non-permanent AF patients receiving AF ablation alone versus concomitant radiofrequency RDN.[11] The ULTRA-HFIB trial (Ultrasound-Based Renal Sympathetic Denervation as Adjunctive Upstream Therapy during Atrial Fibrillation Ablation; NCT04182620) is currently comparing AF ablation with and without ultrasound RDN. These ongoing clinical trials use continuous electrogram monitoring to guarantee quality of both treatment and data collection.

Application in Heart failure

The overactivity of the sympathetic nervous system causes an imbalance in vagal activity and this imbalance of the sympathetic nervous system causes deterioration. Modulation of neurohormone and sympathetic activity by beta-blockers has been a standard of care for preventing mortality, hospitalization, and sudden cardiac death. RDN is expected to intervene in the sympathetic overactivity directly or indirectly and may positively affect heart failure.

The sympathetic nervous system also plays a role in the pathogenesis of ventricular arrhythmias. The efficacy of RDN on ventricular tachyarrhythmia has been reported in several case series and a meta-analysis.[12-16] Several experiences testing RDN in heart failure have been published, suggesting the safety of the procedure and improvement of the left ventricular mass index and exercise capacity.[17-20] One multi-center comparative clinical trial using cardiovascular magnetic resonance imaging demonstrated that RDN improved diastolic function and reduced left ventricular mass.[19] These findings implied that RDN might have benefits in diastolic heart failure. However, the RDT-PEF trial, a single-center randomized clinical trial, enrolled 25 patients with diastolic heart failure. It was terminated early due to difficult recruitment and was underpowered to detect any significant difference of endpoints.[21] Further post-hoc analysis of the RDT-PEF trial also showed RDN had no impact on macro- and microvascular function in heart failure with preserved ejection fraction (HFpEF).[22] A recent retrospective analysis of RDN-treated patients with hypertension and also meeting criteria for HFpEF showed good BP response and evidence of improved aortic mechanical properties and left ventricular filling dynamics.[23]

The SYMPLICITY-HF study, a single-arm prospective cohort study, enrolled 39 patients with heart failure and reduced ejection fraction (HFrEF) who underwent RDN. The primary object was to survey both safety and physiological changes after RDN. The results showed RDN was associated with lowering NT-proBNP and improving glucose intolerance. However, no improvement of ejection fraction was observed in 12 months.[24] The RE-ADAPT-CHF, which plans to enroll 100 patients, has been designed to investigate effects on arrhythmia burden and cardiac and renal function as the main safety and efficacy endpoints by using a 1st generation RDN catheter. The trial is currently being conducted. In 2020, a meta-analysis pooled five single-center randomized clinical trials to investigate the efficacy of RDN in HFrEF. The results showed RDN improved left ventricular function, 6-minute walk distance, and BNP levels.[25] Another meta-analysis pooled 11 both randomized controlled studies and self-controlled studies, with results similar to the previous meta-analysis, with improved left ventricular function and decreased BNP levels.[26] The use of RDN to treat heart failure was found to be both safe and effective in meta-analyses and small RCTs. Some clinical trials (NCT01870310, NCT01402726, NCT01639378, NCT01790906) are still ongoing to investigate the effect of RDN on chronic heart failure. The evidence provides a rationale to conduct a large-scale randomized trial in the future.

Application in obstructive sleep apnea

OSA is characterized as repeated obstruction of the upper airway, resulting in intermittent hypoxemia. It leads to an increase in sympathetic nervous system activity and causes resistant hypertension. Moreover, sympathetic overactivity influences the genioglossal nerve, which mediates the upper airway muscle and causes dilatation of the upper airway. Excessive sympathetic activity induces pharyngeal wall thickening and worsens OSA.[27,28] OSA is a contributing factor to hypertension, especially in resistant hypertension. The prevalence of hypertension in OSA patients is up to 35%, of which 60% to 80% have drug-resistant hypertension. Besides, OSA is one of the most common comorbidities of hypertension and diabetes in Asians despite comparatively lower body weight. Three early case series studies demonstrated that RDN had a trend to reduce blood pressure and apnea-hypopnea index (AHI) in patients with hypertension and OSA.[29-31] However, one case-control study showed that RDN did not affect blood pressure in drug-resistant hypertension patients with untreated OSA.[32] One meta-analysis enrolled five case-control studies to investigate the effects of RDN in hypertension with OSA. The results showed a significant improvement in blood pressure at six months of follow-up. The subgroup analysis included 49 patients with OSA and found a reduction of AHI in 6 months. Moreover, fewer nocturnal awakenings and improvement of nocturnal oxygen saturation were observed.[33] In the post hoc analysis of the SIMPLICITY HTN-3 study, RDN reduced the 6-month office SBP significantly in OSA subjects (-17.0±22.4 vs. -6.3±26.1 mmHg, p=0.01) but was not effective in those without OSA (p=0.64).[34] Data obtained by Ewa Warchol-Celinska et al. were in concordance with this investigation, suggesting that patients with OSA may be exceptionally responsive to RDN therapy. In this phase II randomized controlled trial with all AHI >15 at baseline, the efficacy of RDN was accompanied by improvement in the severity of OSA.[35] In conclusion, RDN had the effect of reducing both blood pressure and AHI in hypertension subjects with OSA. Further large-scale RCTs are needed to confirm these proof-of-concept data.

Application in diabetes mellitus

In comparison with healthy subjects, age-matched patients with metabolic syndrome had more significant sympathetic nerve activity, irrespective of hypertension.[36] Among patients with type 2 diabetes mellitus, the findings were similar, and the sympathetic drive was even greater if the patients had concomitant hypertension.[37] Since changes in sympathetic nerve activity positively correlated to the changes in blood pressure, RDN was hypothetically able to improve the status of metabolic disorders while reducing sympathetic drive.[36,38]

In 2011, Mahfoud et al. were first to report that fasting glucose, serum insulin, and insulin resistance were all improved in a pilot study among 37 diabetic patients.[39] In 2016, preclinical data also implicated the role of RDN in the regulation of insulin action at the level of the liver to counteract insulin resistance.[40] However, the following three clinical trials produced varying results regarding the impact of RDN on insulin resistance.[41-43] Despite the positive outcomes in pilot studies, the meta-analysis concluded there was no impact on glucose metabolism with catheter-based RDN. This meta-analysis enrolled six randomized controlled studies, one non-randomized controlled study and 12 observational cohort studies; a total of 2245 subjects. The results found no significant change after RDN in fasting glucose, insulin, HbA1c, and C-peptide.[44] Notably, the introduction of a new generation of ablation catheters, longer follow-up, and more restricted study designs (fixed drug regimen and doses) may restrict confounding factors and better illuminate this issue. In summary, based on current evidence, RDN has no impact on glucose metabolism. A more rigorously designed large-scale randomized controlled study is needed.

Application in chronic kidney disease

Patients with eGFR <45 mL/min/1.73 m^2 were excluded from previous clinical trials but may respond to RDN. Clinical evidence has come from patients with end-stage renal disease after nephrectomy, where elevated muscle sympathetic nerve activity is reduced close to normal individuals' levels. The ISAR-denerve trial demonstrated that RDN is efficacious and safe in renal transplant recipients with hypertension.[45] Hering et al. demonstrated the safety of the procedure for those with eGFR 15 to 45 mL/min/1.73 m^2, whereas Kiuchi et al. showed improvement of renal function in patients with mean eGFR 64.2 ± 23.9 mL/min/1.73 m^2 at baseline.[46-48] Considering the efficacy on AF and left ventricular mass index, RDN could also benefit patients either with or without chronic kidney disease, according to several studies.[5,6,49]

The Global SYMPLICITY Registry enrolled a large cohort of patients, both with and without CKD, who were treated with RDN and followed up for 3 years. The results showed both the safety and efficacy of RDN in ambulatory BP reduction after 3 years follow-up.[50,51] Since chronic kidney disease is expected as a cause or comorbidity of hypertension, a large-scale randomized trial investigating the safety and efficacy of RDN in CKD with uncontrolled hypertension is planned, which will enroll 80 patients with CKD stage 3 (RDN-CKD study, NCT04264403) and was started in 2020.

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