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Beyond Blood Pressure: Percutaneous Renal Denervation for the Management of Sympathetic Hyperactivity and Associated Disease States

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Renal artery denervation (RDN) is a catheter-based technique designed to decrease renal sympathetic nervous system (SNS) signaling and return the body to more physiological homeostasis. Preliminary investigations suggested an excellent therapeutic profile in resistant hypertension,[1,2] but results from SYMPLICITY HTN-3, a randomized control trial (RCT) of RDN in treatment-resistant hypertension using a sham control procedure, surprisingly contradicted prior results and suggested no benefit with RDN.[3] There is significant speculation regarding explanations for this result, and forthcoming data from a large global registry continue to suggest actual benefit with RDN for treatment of hypertension.[4] Some explanations for the failure of SYMPLICITY HTN-3 to reach its primary efficacy end point include potential biases in prior trials and issues that may have affected SYMPLICITY HTN-3, including ineffective denervation, inadequate operator experience, and suboptimal medication compliance.[5] This result highlights the preliminary nature of the data available regarding RDN's clinical effect and the need for carefully designed trials prior to introduction as a therapeutic modality. Preclinical studies and proof-of-concept human trials continue to support the potential use of RDN in the management of multiple disease states characterized by sympathetic overactivation, often independent of antihypertensive effects. The data currently available suffer from the same potential biases as initial studies in hypertension, making the multitude of ongoing clinical trials in these areas crucial for understanding the clinical application of RDN.

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Sympathorenal Axis

SNS activation, the evolutionary backbone of the acute fight-or-flight response, potentiates many diseases through chronic pathological input (Figure 1).[6] These diseases include hypertension, heart failure, arrhythmia, renal insufficiency, and insulin resistance—pathologies that are both causes and consequences of sympathetic hyperactivity.[7] RDN is mechanistically a modulator of the SNS. Anatomically, efferent SNS fibers to the kidney, arising from the second sympathetic ganglion, form a network within the renal artery adventitia.[6] Sympathetic stimulation by the juxtaglomerular apparatus leads to volume retention, sodium resorption, decreased renal blood flow, and renin–angiotensin–aldosterone system activation.[8] Sensory afferent fibers away from the kidney, acting through the posterior hypothalamus, regulate sympathetic outflow to control systemic hemodynamics and reflexive sympathetic efferent activity.[8] Clinically, this systemic balance is exemplified by the contrast between renal transplant and bilateral nephrectomy. During transplant, sympathetic nerves are severed, but prior sympathetic overactivation remains, likely because of continued afferent signaling from the failing native kidney[9]; however, bilateral nephrectomy in end-stage disease, by removing the nidus for sympathetic activation, normalizes central sympathetic outflow.[9] Reciprocal interaction along this loop ideally creates homeostasis, but often it cannot be maintained.

Multiple animal models have demonstrated that renal denervation effectively reduces SNS outflow to the kidney, restoring physiological natriuresis and diuresis and reducing renin release.[10] Early 20th century radical sympathectomy for uncontrolled hypertension had relative success controlling blood pressure (BP), thereby reducing mortality[11,12]; however, these nonselective surgical approaches were associated with significant morbidity, including bowel and bladder

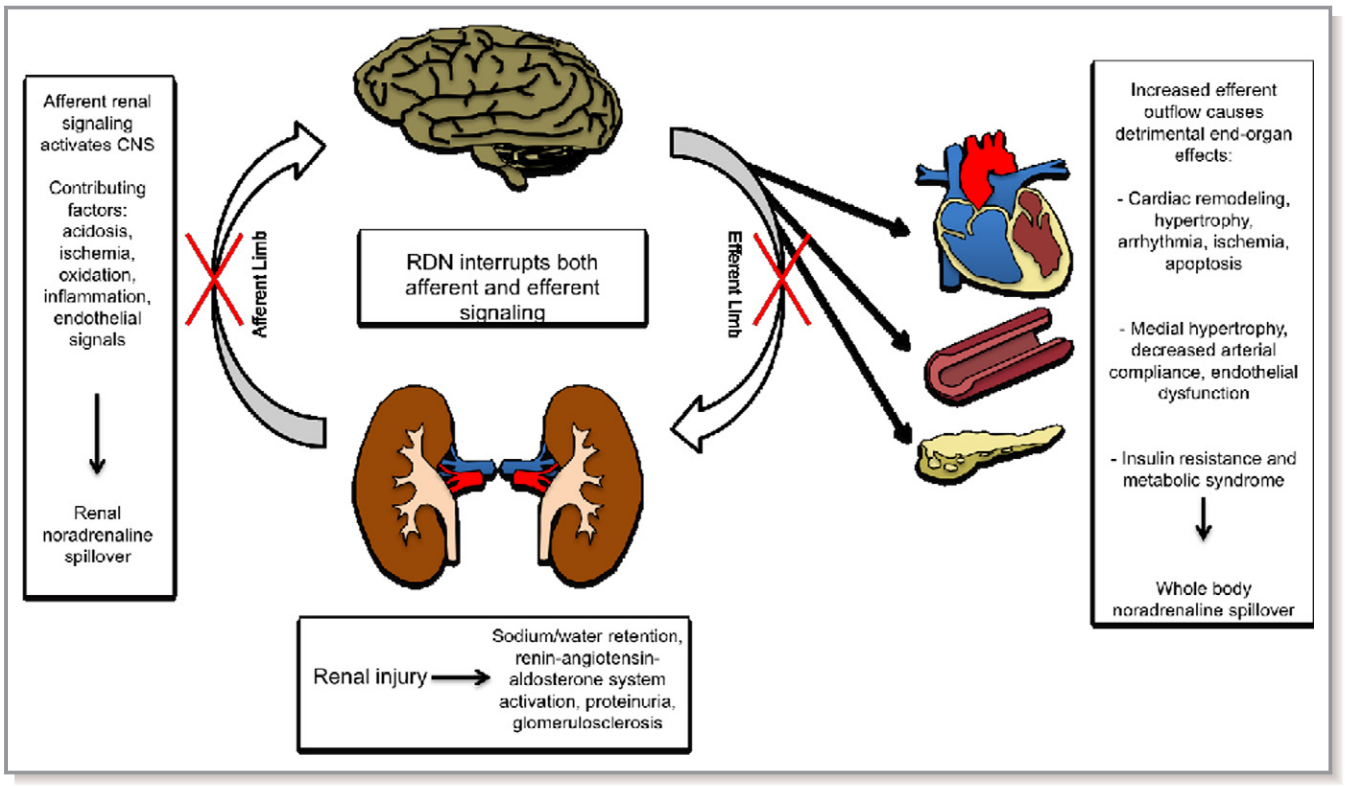

Figure 1. Sympathetic nervous system efferent activity stimulates the heart and arterial vasculature, causing pathological maladaptation. Afferent renal signals, induced by multiple inflammatory mediators, reflexively activate sympathetic outflow. RDN interrupts this pathological cycle. CNS indicates central nervous system; RDN, renal artery denervation.

incompetence, erectile dysfunction, and severe postural hypotension.[11,12] Advances in tolerability and safety afforded by minimally invasive, selective RDN have improved the risk–benefit profile for emerging catheter-based techniques.[1,2,4,7]

In early studies of refractory hypertension, RDN reduced sympathetic hyperactivity. In current studies, SNS activity is measured using noradrenaline spillover and muscle sympathetic nerve activity.[13] Noradrenaline spillover, in which infusions of radiolabeled noradrenaline spill over by avoiding local neuronal uptake, characterizes regional and whole-body sympathetic activity.[14] Muscle sympathetic nerve activity assesses nerve-firing rates to determine sympathetic outflow to muscle motor units.[13] Several initial studies have revealed statistically significant reductions in both noradrenaline spillover and muscle sympathetic nerve activity in patients who have undergone RDN, often independent of antihypertensive effects.[11,13,15] Decreases in sympathetic activity have the potential to positively influence multiple disease states.

Heart Failure

Vascular Stiffness

Although recent results indicate that RDN may not have a significant effect on ambulatory BP, RDN still has potential to modulate vascular stiffness and central hemodynamic regulation because adrenergic mechanisms are closely linked to all aspects of arterial distensibility and compliance.[15,16] Aortic pulse wave velocity and peripheral augmentation index are vascular stiffness measures that correlate with cardiovascular events and mortality and may provide superior assessments of target organ outcomes compared with traditional brachial BP measurement.[17] Initial investigations by Hering et al demonstrated in a cohort of patients with chronic kidney disease (n=15) that RDN led to rapid attenuation of peripheral augmentation index (decreased from 51% to 39% at 3 months, $P<0.01$).[18] This result was replicated in a separate group with resistant hypertension (n=50) with similar results following RDN, including decreased peripheral augmentation index (30.6±23.8% versus 22.7±22.4% at 3 months, $P=0.002$) independent of change in both systolic and diastolic BP or sympathetic nerve-firing reductions.[15] An additional noncomparative series by Brandt et al (n=120) that more comprehensively measured cardiovascular workload parameters reported similar improvements.[16] At 6 months after RDN, aortic augmentation, augmentation index, and mean central aortic BP were all improved. There were additional reductions in pulse wave velocity and both central and peripheral pulse pressures. These changes importantly corresponded to improved cardiac

workload parameters, measured by ejection duration and aortic systolic pressure load. RDN also led to qualitative improvement in radial and central aortic waveform. These changes are difficult to interpret without comparison but suggest a favorable hemodynamic response to RDN.

Systolic Heart Failure

The consistent benefits of pharmacological neurohormonal blockade observed in clinical trials of systolic heart failure support the primacy of sympathetic activation in progression of ischemic and nonischemic dilated cardiomyopathies; however, the role of SNS activity in reacting to versus precipitating and worsening systolic heart failure is unclear and raises legitimate questions about potential treatment benefit. Multiple animal models simulating heart failure report success using RDN to limit these pathological sympathetic responses.[19] Indirect clinical evidence in humans also supports potential benefit, although results of active clinical trials are needed to assess true clinical impact.[19] These implied benefits correlate to significant outcomes because renal sympathetic activation is a strong negative predictor of progression to heart transplantation and all-cause mortality in systolic heart failure.[20] Despite this strong correlation, no data link reduced SNS activation with clinical benefit.[21]

Two pilot studies demonstrate potential for RDN in systolic heart failure. The Renal Artery Denervation in Chronic Heart Failure (REACH) study assessed RDN safety in 7 patients with New York Heart Association (NYHA) class III to IV heart failure with left ventricle (LV) ejection fraction 28% to 58% without hypertension.[22] At 6 months after the procedure, there were no major adverse events, and benefit was reported for important clinical parameters including increased 6-minute walk (221±33 to 249±34 months, P=0.03) and decreased diuretic requirement in 4 patients (P=0.046). No comparator group is available to assess the significance of these poorly powered results, but a larger randomized extension study is currently ongoing (Table).[23] The Olomouc pilot study investigated patients with NYHA class II to IV heart failure (n=51) randomized to RDN versus optimal medical therapy.[24] The RDN group had a lower incidence of hospitalization (31% versus 72%, P<0.001) and improved NYHA class, decreased NT-pro brain natriuretic peptide, and improvements in numerous echocardiographic parameters. These results merit considerable scrutiny in light of previous data regarding sympathetic manipulation in heart failure, including the 1934 patient MOXCON RCT, which surprisingly demonstrated increased mortality in patients with systolic heart failure using the central sympathetic inhibitor minoxidine.[21] Additional RCTs investigating long-term effects of RDN in systolic heart failure on cardiovascular events and mortality will hopefully provide clarity as to RDN's effect in this area (Table).[23]

Heart Failure With a Preserved Ejection Fraction

LV hypertrophy; LV diastolic dysfunction; and the clinical correlate, heart failure with a preserved ejection fraction, result from sympathetic overactivity, with important implications for cardiovascular outcomes including independent associations with mortality.[25] Adrenergic tone is predictive of LV mass and is associated with both LV hypertrophy and diastolic dysfunction.[25] These changes may ultimately cause cardiac fibrosis, resulting in impaired ventricular relaxation and heart failure with a preserved ejection fraction.[25] In practice, however, these end-organ effects are primarily the result of long-standing hypertension, and distinguishing benefit outside of that associated with BP reduction presents a constant confounder.

Preliminary reports suggest that RDN may limit this pathology. In an RCT of patients with refractory hypertension (n=64), one quarter of whom clinically had heart failure with a preserved ejection fraction,[1] Brandt et al reported improvements in echocardiographic correlates of LV hypertrophy and stiffness. Compared with optimal medical therapy, at 6 months after RDN treatment, there was a 17% reduction in LV mass with treatment alone (decrease of 53.9±15.6 to 44.7±14.9 g/m$^{2.7}$, P<0.001), most prominently in a cohort with baseline LV hypertrophy.[25] Systolic function likewise improved from baseline in the RDN group, with reduced LV end-systolic volume and increased ejection fraction (63.1±8.1% to 70.1±11.5%, P<0.001). Diastolic dysfunction, as measured by shortened mitral E-wave deceleration time, decreased isovolumic relaxation time, increased diastolic relaxation on lateral mitral tissue Doppler, and decreased mitral inflow:annular velocity ratio, likewise improved from baseline in the treatment group alone (Figure 2).[25] A multicenter, blinded control trial by Mahfoud et al (n=72) of similar patients used cardiac magnetic resonance imaging to assess effects of RDN on LV hypertrophy and stiffness.[26] Cardiac magnetic resonance imaging is a modality with less interobserver variability than echocardiography, increasing precision and sensitivity.[26] At 6 months after RDN, LV mass index was reduced by 7.1% (decrease of 46.3±13.6 to 43±12.6 g/m$^{2.7}$, P<0.001) in the treatment group. This represents a similar but smaller degree of LV mass reduction than in the aforementioned echocardiographic study, underscoring potentially increased specificity of imaging and bias in the these smaller, preliminary studies.[27] Systolic function, specifically in patients with baseline reduction in ejection fraction, also increased following RDN (ejection fraction 43% versus 50%, P<0.001). RDN also improved diastolic dysfunction, with a 21% increase in proportion of patients with reduced LV circumferential

Table. Sample of Current Randomized Trials Assessing Effect of RDN in Various Diseases

Title	Comparison Groups	Sample Size*	Start Date to End Date*	Primary End Point (Follow-up Interval)	Major Inclusion Criteria
Heart failure					
RDN in patients with heart failure	RDN vs OMT	200	7/2011 to 4/2017	CV events, death (36 months)	NYHA II to IV, EF ≤40% or ≥45% with HFPEF
RDN in chronic heart failure study (REACH)	RDN vs sham procedure	100	8/2012 to 8/2014	Symptoms (12 months)	NYHA II+, EF ≤40%
RDN for patients with chronic heart failure (RSD4CHF)	RDN+conventional therapy vs conventional therapy	200	1/2013 to 4/2017	All-cause mortality, CV events (24 months)	NYHA II to IV, EF <≤5% for >6 months
RDN in patients with heart failure and severe LV dysfunction (Olomouc)	RDN+OMT vs OMT	50	6/2012 to 6/2016	NT-proBNP (6 and 12 months)	NYHA II to IV, EF ≤35%
RDN in HFPEF (RDT-PEF)	RDN vs control	40	4/2013 to 4/2016	Symptoms, BNP, echocardiographic parameters (12 months)	HFPEF with NYHA II to III, EF >50%
Denervation of renAl sympathetIc nerveS in hearT Failure With nOrmal Lv EF (DIASTOLE)	RDN vs OMT	60	4/2012 to 12/2014	E/E' change (12 months)	Heart failure symptoms, EF ≥50%, LV diastolic dysfunction
Atrial fibrillation					
Concomitant RDN therapy in hypertensive patients undergoing AF ablation	PVI+RDN vs PVI	40	9/2013 to 9/2016	AF recurrence/burden (12 months)	pAF or persAF ablation-eligible, ≥2 antihypertensives
Adjunctive RDN to modify hypertension as upstream therapy in treatment of AF (H-FIB)	Catheter ablation+RDN vs catheter ablation	300	9/2012 to 7/2017	AAD-free single procedure AF freedom (12 months)	pAF/persAF, planned ablation, ≥1 antihypertensive
CPVI plus RDN vs CPVI alone for AF ablation	Circumferential PVI+RDN vs circumferential PVI	100	6/2012 to 12/2016	Relapse atrial tachyarrhythmia >30 seconds (4 years)	pAF/persAF, failure of ≥1 AAD
RDN in patients with drug-resistant hypertension and symptomatic AF (RSD for AF)	RDN vs OMT	200	7/2012 to 7/2015	AF burden (12 months)	pAF/persAF systolic BP >160 mm Hg on 3+ antihypertensives
RDN in patients with hypertension and paroxysmal AF (RSD for pAF)	RDN vs OMT	100	7/2012 to 6/2015	AF burden (12 months)	pAF (<7 days), hypertension ≥6 months
RDN in addition to catheter ablation to eliminate AF (ERADICATE–AF)	PVI+RDN vs PVI	300	6/2013 to 6/2014	AAD-free AF recurrence (12 months)	pAF (<7 days), ≥1 antihypertensive

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Table. Continued

Title	Comparison Groups	Sample Size*	Start Date to End Date*	Primary End Point (Follow-up Interval)	Major Inclusion Criteria
Combined treatment of arterial hypertension and AF	Circumferential PVI+RDN vs circumferential PVI	60	4/2012 to 6/2013	Recurrence atrial tachyarrhythmia >30 seconds AAD-free single ablation (12 months)	Symptomatic AF, failure of ≥2 AADs, ≥3 antihypertensives
Ganglionated plexi ablation vs RDN in patients undergoing PVI	PVI+RDN vs PVI+Ganglionated plexi ablation	80	6/2012 to 6/2013	AF/arrhythmia freedom (12 months)	Symptomatic AF, failure of ≥2 AADs, ≥1 antihypertensive
Feasibility study to evaluate effect of concomitant RDN and cardiac ablation on AF recurrence	Cardiac ablation vs cardiac ablation+RDN	100	7/2013 to 5/2016	AF freedom (12 months)	pAF/persAF ablation-eligible, ≥3 antihypertensives
Combined AF ablation and RDN for maintenance of sinus rhythm and management of resistant hypertension	RDN+PVI vs PVI	40	1/2014 to 1/2019	BP (1 and 3 months)	AF scheduled for ablation, ≥1 antihypertensive
Comparison of redo PVI with vs without RDN for recurrent AF after initial PVI	Redo PVI+RDN vs redo PVI	60	9/2013 to 9/2016	AF freedom (12 months)	pAF with PVI within 2 years, recurrent symptoms, ≥2 antihypertensives
Ventricular tachycardia					
RDN to suppress ventricular tachyarrhythmias (RESCUE-VT)	ICD+RDN vs ICD	220	10/2012 to 10/2015	Time to first ICD event or incessant VT (1, 6, 12, 18, 24 months)	Planned ICD implantation, structural heart disease
RDN as adjunct to catheter-based VT ablation (RESET-VT)	VT ablation+RDN vs VT ablation	202	3/2013 to 11/2016	Time to first ICD event or incessant VT (1, 6, 12, 18, 24 months)	Planned VT ablation, structural heart disease
Chronic kidney disease					
RDN in patients with chronic renal failure	RDN vs OMT	200	8/2011 to 8/2016	Hemodialysis, uremia incidence (36 months)	eGFR >45, renal damage by urine microalbumin, 24-h urine protein, or urine microalbumin/creatinine
RDN in patients with chronic kidney disease and resistant hypertension (RSD4CKD)	RDN+OMT vs OMT	100	11/2012 to 4/2018	All-cause mortality, creatinine doubling, end-stage disease (36 months)	Creatinine 1.5 to 5.0, proteinuria, or nondiabetic nephropathy
Randomized safety and efficacy study investigating the effects of catheter-based RDN in patients after renal transplantation	RDN vs OMT	40	7/2013 to 7/2014	BP, medication change, GFR, renovascular safety (6 months)	Renal transplant
RDN for ADPKD BP and disease progression control (RAFALE)	RDN vs antihypertensives	100	8/2013 to 7/2015	Systolic BP (12 months)	ADPKD

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Table. Continued

Title	Comparison Groups	Sample Size*	Start Date to End Date*	Primary End Point (Follow-up Interval)	Major Inclusion Criteria
Metabolic disease					
RDN in patients with diabetic nephropathy and persistent proteinuria (DERENEDIAB)	RDN+TMNS† vs TMNS	120	4/2012 to 4/2015	Proteinuria/creatinuria ratio (12 months)	Diabetic nephropathy, protein/creatinine >0.1
RDN and insulin sensitivity (RENSYMPIS)	RDN vs OMT	60	1/2013 to 1/2016	Systolic BP (24 months)	
RDN for treatment of metabolic syndrome-associated hypertension (Metabolic Syndrome Study)	RDN vs no RDN	60	9/2013 to 1/2015	Insulin resistance change (3 months)	Metabolic syndrome
RDN in patients with metabolic syndrome	RDN vs OMT	200	8/2011 to 8/2016	CV events, death (36 months)	Metabolic syndrome
Effects of RDN on BP and clinical course of obstructive sleep apnea in patients with resistant hypertension	RDN+OMT vs RDN	60	7/2011 to 12/2014	BP (3 months)	Obstructive sleep apnea
Myocardial ischemia					
RDN in patients after acute coronary syndrome (ACSRD)	PCI vs PCI+RDN in acute coronary syndromes	80	6/2013 to 6/2016	CV death, MI, stroke, revascularization (12 months)	Unstable angina/non-ST-elevation MI or stenosis
RDN as secondary prevention for patients after PCI (RSD4CHD2PRE)	RDN+PCI+OMT vs PCI+OMT	600	11/2012 to 7/2015	All-cause mortality (24 months)	Not specified

Only randomized trials listed. All trials include additional information at http://www.clinicaltrials.gov. AAD indicates antiarrhythmic drug; ADPKD, autosomal dominant polycystic kidney disease; AF, atrial fibrillation; BP, blood pressure; CPVI, circumferential pulmonary vein isolation; CV, cardiovascular; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HFPEF, heart failure with a preserved ejection fraction; ICD, implantable cardioverter-defibrillator; LV, left ventricle; MI, myocardial infarction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; OMT, optimal medical therapy; pAF, paroxysmal atrial fibrillation; PCI, percutaneous coronary intervention; persAF, persistent atrial fibrillation; PVI, pulmonary vein isolation; RDN, renal artery denervation; VT, ventricular tachycardia.

*Anticipated.

†TMNS, standardized antiproteinuric regimen.

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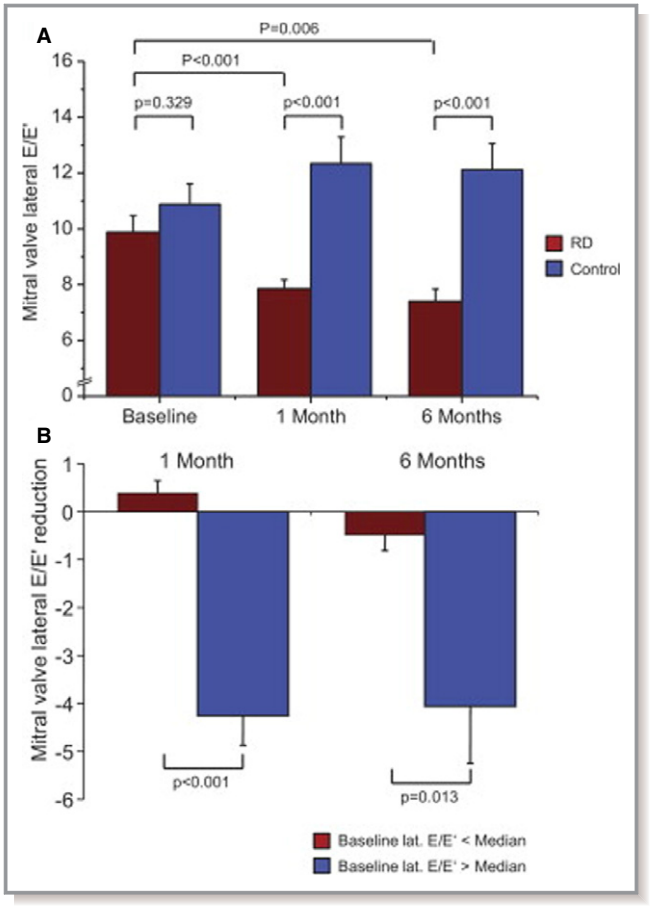

Figure 2. Effect of renal artery denervation (RDN) on diastolic function. A, Mitral valve lateral E/E′ at baseline, 1 month, and 6 months in RDN and control patients. Although no significant changes could be detected in the control group, E/E′ significantly decreased in the RDN group. In the treatment group, *P* for trend was <0.001. B, Differential effect of RDN on E/E′ reduction depended on the degree of diastolic dysfunction at baseline. Reduction of E/E′ by RDN was significantly greater in those patients with an E/E′ above the median of 8.8 at baseline. Values are presented as mean±SE. Reproduced with permission from Brandt et al.[25]. RD indicates renal denervation.

strain.[26] These results are susceptible to difficulties similar to those in studies examining hypertension, including difficulty maintaining control groups, medication compliance, and matching for baseline variables such as BP.[27] In light of these preliminary results, 2 large RCTs will compare the effects of RDN and optimal medical therapy on imaging end points, hemodynamics, exercise capacity, and quality of life in heart failure with a preserved ejection fraction (Table).[23]

Arrhythmias

Atrial Fibrillation

Atrial fibrillation (AF) and other cardiac dysrhythmias result from complex electrophysiological interactions influenced by the autonomic nervous system and varied hemodynamic conditions.[28,29] Both hypertension and autonomic imbalance contribute to arrhythmogenic structural remodeling of the left atrium, leading to local conduction disturbances that create the substrate and precipitant for AF.[29] Beta-adrenergics increase AF incidence, whereas beta-blockade reduces recurrence.[28] In contrast, enhanced vagal tone shortens the atrial effective refractory period, potentially inducing and maintaining AF.[30] The relationship to autonomic control is complex and likely involves imbalanced sympathetic and parasympathetic input.[30]

RDN decreased rates of AF inducibility in both a normotensive porcine model comparing carotid baroreflex stimulation and atenolol with RDN and a canine model of pacing-induced heart failure.[30–32] In humans, Pokushalov et al reported a small cohort (n=27) of moderately hypertensive patients with AF treated with pulmonary vein isolation (PVI) alone and in combination with RDN, resulting in decreased AF relapse with RDN plus PVI compared with PVI alone (69% versus 29%, *P*=0.033).[28] Limitations of this trial include change in primary end point and small sample size.[33] A recent 2-study meta-analysis of these data and a similar trial in severe resistant hypertension reported similar results, with decreased AF relapse with RDN plus PVI compared with PVI alone (62% versus 41%, *P*=0.014) (Figure 3), with greater effect reported for the combination of persistent AF and severe hypertension (hazard ratio for RDN plus PVI versus PVI alone: 0.25).[34] Many ongoing RCTs are currently examining the efficacy and safety of RDN as adjunctive treatment with PVI and other modalities for the management of AF (Table).[22]

Ventricular Tachyarrhythmias

Ventricular tachyarrhythmias are prominent after ischemic insult, potentially driven by central sympathetic hyperactivity.[32] Initiation of beta-blockers to prevent ventricular tachyarrhythmias is standard postmyocardial infarction practice, and RDN may play a similar role in autonomic modulation.[35] Radical interventions, including surgical cardiac sympathetic denervation, have even been considered for patients with refractory ventricular tachycardia.[36] A porcine model of acute coronary ischemia demonstrated significant suppression of ventricular arrhythmia (86% versus 17%, *P*=0.029) using RDN compared with a sham procedure after ischemia and an equivalent effect to treatment with atenolol.[35] The potential of RDN to suppress ventricular tachycardia in humans has been explored thus far only in case reports and small series but suggests decreases in premature ventricular contractions, decreased ventricular tachycardia burden, and increased ventricular tachycardia–free intervals in a variety of clinical situations including dilated and hypertrophic cardiomyopathy and refractory ventricular tachycardia and after myocardial

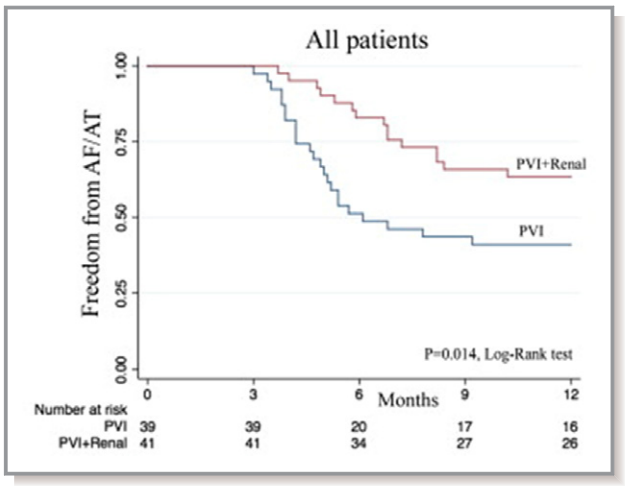

Figure 3. Incidence of atrial fibrillation (AF) recurrences in all patients with and without renal artery denervation. AT indicates atrial tachycardia; PVI, pulmonary vein isolation. Reproduced with permission from Pokushalov et al.[34]

infarction.[36,37] Two currently enrolling RCTs will address the use of RDN in patients susceptible to ventricular tachyarrhythmias (Table).[23]

Chronic Kidney Disease

SNS activation is a hallmark of severe chronic kidney disease, with the degree of activation directly correlated to adverse cardiovascular prognosis.[38] RDN, which directly manipulates the renal arteries, is generally considered safe in this population, as demonstrated by a pooled analysis documenting only a single renal artery dissection in 149 patients, without hemodynamic, electrolyte, or renal function disturbances.[2] Initial investigations in patients with resistant hypertension and preserved renal function showed that RDN has a generally neutral effect on glomerular filtration rate (GFR).[11] In patients with lower baseline GFR, these studies raised concern about worsening renal function following RDN, an effect not seen in continued follow-up. Hering et al reported that in a small cohort (n=15) with moderate to severe chronic kidney disease (GFR<45 mL/min per 1.73 m^2), RDN led to overall improvement in hemodynamic and functional parameters from baseline, without change in GFR, serum or urine biochemistries, or volume status at 6 months.[18] This stability accompanied hemodynamic improvement, with restoration of physiological dipping patterns and reduced augmentation index. An additional cohort with multiple causes of end-stage renal disease (hemodialysis dependence ≥6 months) indicated the potential of RDN to reduce hypertension in this group without major adverse events.[39] These results are clouded by increased anatomical and procedural complications in this cohort that may limit practical therapeutic applications.[40] In addition, both of these studies examined small uncontrolled cohorts, and large-scale data regarding safety of RDN in chronic kidney disease are needed. In a series of patients with resistant hypertension (n=62), Dörr et al demonstrated no significant change in sensitive biomarkers of renal structural and functional damage (neutrophil gelatinase–associated lipocalin and kidney injury molecule 1) at both 48 hours and 3 months after RDN.[41] This included a cohort (n=8) with chronic kidney disease (GFR<45 mL/min per 1.73 m^2) and was correlated with stability of estimated GFR, urea nitrogen, and serum creatinine, providing additional evidence of the safety of RDN for renal function.[41]

Although RDN appears well tolerated by the kidneys, the additional benefit to this system remains less clear. In a prospective study of patients with resistant hypertension (n=100), Mahfoud et al reported that RDN led to baseline improvement in renal resistive index, an ultrasonographic marker of hypertension duration and severity associated with decreased renal function.[42] Renal filtration was also improved, as shown by reduced micro- and macroalbuminuria (−10% and −23% from baseline, respectively; P=0.001), without significant change in GFR. Ott et al recently demonstrated similar improvement in glomerular filtration at 6 months after RDN in a cohort of patients with resistant hypertension (n=59).[43] Serum renal function remained unchanged, whereas the urinary albumin:creatinine ratio was reduced (160 versus 89 mg/g, P<0.001), an effect observed in populations with both baseline micro- and macroalbuminuria. Although this promising suggestion for improvement merits attention and continued investigation, it is not a result that is consistently documented in initial trials of resistant hypertension and suffers from the same pitfalls as these early trials. In addition, given the direct relationship between glomerular filtration and BP, this derived improvement in renal function may be more related to effects of BP reduction than sympathetic modulation. Ongoing trials will build on these data, examining the effect of RDN on renal function in patients with chronic kidney disease, diabetic nephropathy, renal transplantation, and polycystic kidney disease (Table).[23]

Insulin Resistance

SNS activation promotes glucose availability, increasing lipolysis and hepatic gluconeogenesis and decreasing insulin secretion.[44] In turn, insulin resistance mediates excess adrenergic drive, establishing a perpetuating cycle.[44] This creates an environment of inflammation and oxidative stress present in half of patients with resistant hypertension.[45] Preliminary evidence suggests that RDN may help re-establish metabolic balance and attenuate insulin resistance. A prospective study (n=50) by Mahfoud et al demonstrated significantly reduced

fasting glucose, serum insulin, and C-peptide levels and improved insulin sensitivity with RDN compared with control at 3 months (Figure 4).[45] A small prospective study of patients with sleep apnea (n=10) similarly demonstrated significant reductions in post–oral glucose tolerance hyperglycemia and long-term glycemic control, as measured from baseline hemoglobin A1c 6 months after RDN (median 6.1% to 5.6%, $P<0.05$).[46] Similar improvement was noted in a case series (n=2) of polycystic ovarian syndrome, a condition characterized by adrenergic excess and metabolic derangement.[44] RDN improved a broad array of end points including insulin sensitivity and even return of physiological menstruation in 1 patient despite a prior amenorrheic period of 3 years.[44] These results have sparked great interest in the role of RDN as a metabolic regulator, with RCTs under way to assess this effect (Table).[23]

Obstructive Sleep Apnea

Sleep apnea is an independent cardiovascular risk factor characterized by recurrent upper airway obstruction and intermittent hypoxia stimulating SNS activity, causing systemic inflammation and endothelial dysfunction.[47] Two groups demonstrate an additive sympathostimulating effect of sleep apnea in patients with metabolic syndrome.[47] Hypothesis-generating studies suggest a benefit of RDN in sleep apnea, but current data are limited in both power and scope; larger studies, such as those that are ongoing (Table),[23] are needed to truly characterize the effect of RDN in sleep apnea. In a prospective study of patients with sleep apnea (n=10), Witkowski et al reported that RDN decreased apnea–hypopnea index (median 16.3 versus 4.5 events per hour, $P=0.059$) and subjective sleepiness.[46] A retrospective analysis (n=31) comparing RDN with continuous positive airway pressure in patients with moderate to severe sleep apnea also demonstrated improvement in sleep parameters (nocturnal apnea–hypopnea index and duration SpO_2 <90%) with both RDN and continuous positive airway pressure, but more significant improvement was noted in the continuous positive airway pressure group.[48]

Myocardial Ischemia and Stroke

Although there are no human clinical data on the role of RDN in myocardial ischemia and stroke, multiple preclinical models and case reports have demonstrated potential benefits. Such

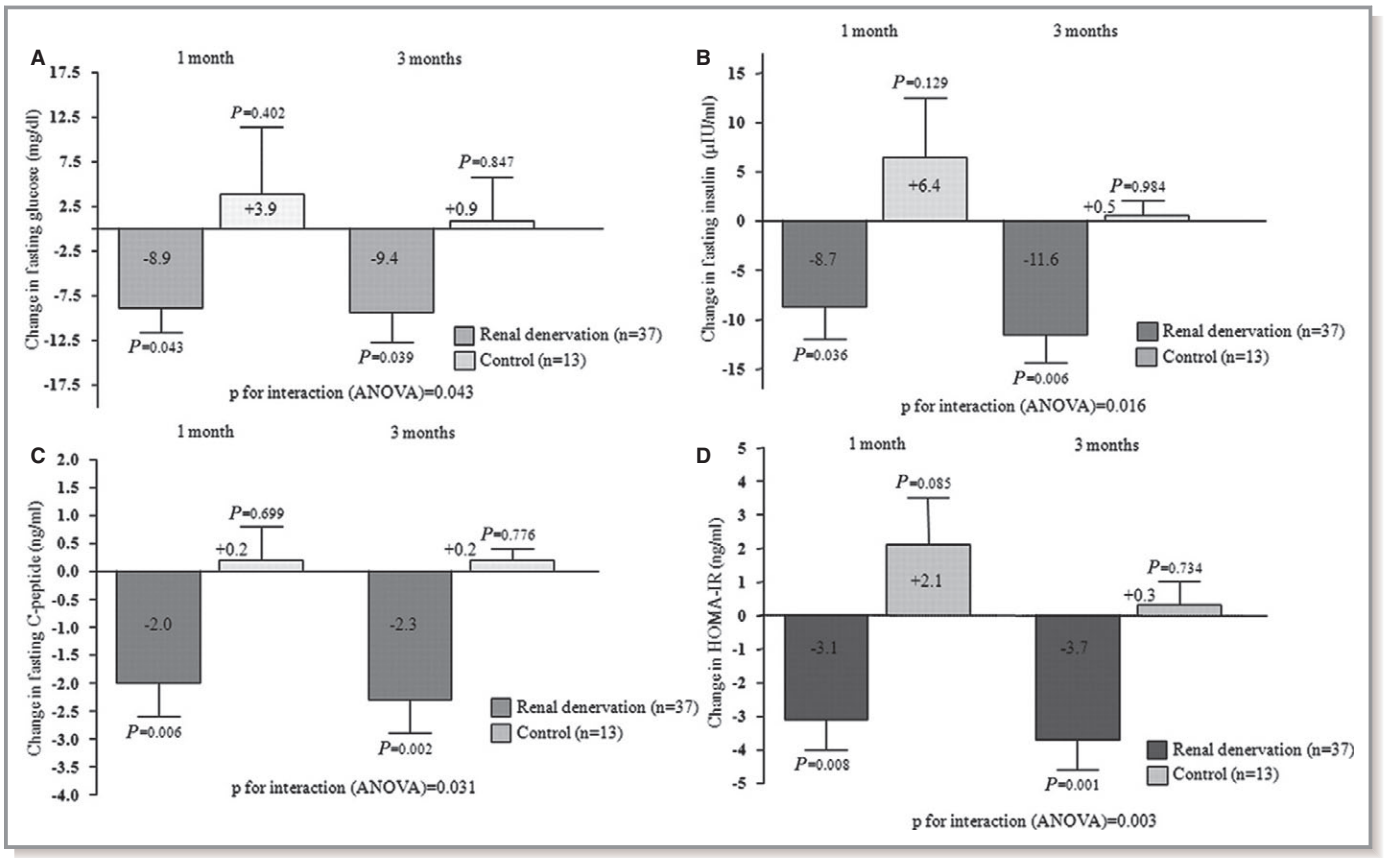

Figure 4. Change (SEM) in fasting glucose (A), fasting insulin (B), C-peptide (C), and homeostasis model assessment—insulin resistance (HOMA-IR) (D) at 1 month and 3 months compared with baseline. *P* values refer to change compared with baseline. Between-group effects, measured by 2-way repeated measures ANOVA, are given as *P* for interaction. Reproduced with permission from Mahfoud et al.[45]

benefits include preventative preservation of cardiac function, noted in 2 models of induced coronary ischemia pretreated with RDN,[35,49] and benefit up to 7 days after ischemia in a rat model that also demonstrated improved hemodynamics and organ perfusion after RDN.[49] Similar end-organ benefit was noted in a high-salt–loaded, hemorrhagic stroke–prone, hypertensive rat model in which RDN, compared with both hydralazine and a sham procedure, reduced neurological deficit and brain injury and attenuated other common poststroke physiological changes.[50] Multiple RCTs are under way applying the conclusions of these models to patients to assess RDN's effect on modulation of physiological deterioration in these conditions of major morbidity and mortality (Table).[23]

Conclusions

RDN moderates the SNS to improve physiological parameters in many chronic diseases. Despite the recent failure of SYMPLICITY HTN-3 to reach its primary end point, burgeoning evidence in many alternative areas suggests the potential to overcome current therapeutic hurdles. Preliminary data continue to support the use of RDN to regulate SNS-derived pathology, with suggestions for benefit outside of strictly antihypertensive effects. Akin to initial results in resistant hypertension, lack of adequate sample size and controls limits interpretation and application of these results. Recent experience highlights their precursory nature and need for more formal exploration. Currently, >100 registered RCTs (Table)[23] are designed to address these questions and formulate new avenues of inquiry.

Disclosures

Dr McArdle and Dr deGoma declare no competing interests. Dr Cohen, Dr Townsend, Dr Wilenky, and Dr Giri were investigators for the Medtronic SYMPLICITY HTN-3 study. They received no compensation for this work.

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