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Renal Denervation for Patients With Atrial Fibrillation

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Abstract

Purpose of Review During the last decade, several case series and small reports have indicated that pulmonary vein isolation (PVI) in combination with renal denervation (RDN) may increase the rate of atrial fibrillation (AF) freedom in patients with hypertension. We aimed to provide a contemporary systematic overview on the techniques, and the efficacy/safety of RDN on AF recurrence, and the current landscape of ongoing investigation.

Recent Findings The recent Evaluate Renal Denervation in Addition to Catheter Ablation to Eliminate Atrial Fibrillation (ERADICATE-AF) trial has demonstrated convincingly that among patients with paroxysmal AF and poorly controlled (but not "resistant") hypertension, RDN added to catheter ablation, compared with catheter ablation alone, significantly increased the likelihood of freedom from AF at 12 months.

Summary RDN has proven to be a unique, effective and safe interventional therapy for the management of AF. Future investigation will likely focus on confirming current findings; expanding the population of eligible patients (eg., non-hypertensives, well controlled hypertensives); determining long-term maintenance of effect and therapeutics.

Keywords Renal denervation · Atrial fibrillation · Hypertension · Recurrence · Ablation · Renal sympathectomy

Introduction

It has long been established that the autonomic nervous system plays an important role in the pathogenesis and maintenance of atrial and ventricular arrhythmias [1]. Indeed, antiadrenergic interventions, such as left cardiac sympathetic denervation, were successfully deployed in patients with long-QT syndrome and later in patients suffering from catecholaminergic polymorphic ventricular tachycardia. These early strategies were demonstrated to be effective in reducing sympathetic activity and to protect against ventricular arrhythmias [2, 3]. Nevertheless, this surgical approach has been used sparingly due to a high incidence of often debilitating side effects, a significant proportion of nonresponders, and procedural complications [4, 5]. However, the concept of decreased sympathetic activity remained an important objective in the prevention and treatment of arrhythmias, most commonly by drug therapy with β-blockers.

Atrial fibrillation (AF) is the most common treated cardiac arrhythmia, and hypertension is one of the most prevalent risk factors for the development of AF. The combination of both diseases is significantly associated with increased morbidity and mortality and exerts an adverse impact on patients' quality of life [6]. Although antiarrhythmic drug therapy is often initially employed, the results are often inadequate. Catheter ablation via pulmonary vein isolation (PVI) has been established as the cornerstone interventional strategy for a variety of patients with AF, yet the recurrence rate remains significant and can occur throughout follow-up in many higher-risk patients [7].

In patients with resistant hypertension, renal denervation (RDN), a form of catheter ablation, was associated with a significant reduction of central sympathetic activity and blood pressure [8, 9]. Although the SYMPLICITY HTN-3 randomized trial failed to show an additional benefit of this strategy when compared with a sham procedure, recent smaller studies

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with better selection designs and a more limited scope have shown statistically significant antihypertensive effects associated with RDN [10–12]. The renal afferent nerves are one of the main regulators of central sympathetic tone, and as such, opens the possibility for RDN to modulate sympathetic activity, yet without affecting peripheral chemoreceptors and mechanoreceptors in the heart and other organs. In prior studies, RDN was shown to reduce heart rate in humans and lower inducibility of AF as well as the ventricular response rate during AF in experimental studies [13, 14].

During the last decade, several case series and small reports have indicated that PVI in combination with RDN may increase the rate of AF freedom in patients with resistant hypertension. The recent Evaluate Renal Denervation in Addition to Catheter Ablation to Eliminate Atrial Fibrillation (ERADICATE-AF) trial has demonstrated convincingly that among patients with paroxysmal AF and poorly controlled (but not "resistant") hypertension, RDN added to catheter ablation, compared with catheter ablation alone, significantly increased the likelihood of freedom from AF at 12 months [15••]. At present, there are additional larger studies that may extend the indications for RDN as a therapeutic option in patients with AF. In this review we will discuss the current techniques, the recent published findings, and the current landscape of ongoing investigation.

RDN–Technical Options

In the past, and prior to the widespread availability and success of pharmacological treatment for resistant hypertension, surgical subdiaphragmatic splanchnicectomy was explored as a therapeutic intervention for malignant hypertension. Sympathetic outflow was interrupted by sectioning both the splanchnic nerve and thoracic dorsal sympathetic chain, resulting in lower blood pressure and systemic vascular resistance [16]. However, the nonselective nature of the procedure produced common side effects such as postural-hypotension, hyperhidrosis, sensory and sexual dysfunction, and depression, therefore the surgical approach was largely abandoned after the introduction of newer antihypertensive medications.

Nevertheless, the control of hypertension remained poor in many patients, carrying a remarkable cardiovascular risk, which highlighted the need for alternative therapeutic strategies leading to the development of the catheter-based interventional approach such as RDN.

To-date, several technologies have been introduced to perform percutaneous RDN. These include the use of catheter-directed radiofrequency ablation, ultrasonic ablation therapy, and pharmacological ablation that is locally delivered through infusion catheters [17].

Catheter-Directed Radiofrequency Ablation

In 2009, Krum et al. published their results of the first trial of catheter-directed RDN using radiofrequency energy. In a proof-of-principle trial, percutaneous radiofrequency ablation was shown to cause substantial and sustained reduction in blood pressure without serious adverse events in patients with resistant hypertension [18].

We have utilized standard cardiac ablation catheter systems, rather than dedicated RDN systems. Using the femoral artery for access, an endovascular catheter was inserted into the renal artery through a guide sheath. If available, real-time 3-dimentional aorta-renal artery maps can be constructed with the use of an ablation catheter and an electroanatomic navigation system. The catheter is positioned toward the distal part of the renal artery and several radiofrequency ablation treatments are applied to the endoluminal surface in a circumferential fashion as the catheter is withdrawn proximally, spacing each treatment by approximately 5 mm [19]. The spiral circumferential pattern ensures the entire circumference of the artery to be treated, but not at same level to avoid stenosis. Approximately 5 to 6 applications of ablation therapy are delivered. This has been shown to cause only a minimal disruption of the renal artery external elastic lamina while providing fibrosis of 10%–25% to the total media and adventitia tissue with no angiographic or histologic arterial stenosis or thrombosis, potential complications [20]. To confirm RDN, high-frequency stimulation can be performed before the initial and after each radiofrequency delivery within the renal artery. The criterion for success is usually met when the sudden increase of blood pressure of about 15 mm Hg is eliminated or greatly reduced.

Results from the pioneering study described earlier led to the development of 4 catheter-directed radiofrequency ablation technologies which were subsequently used in a variety of international prospective clinical trials. These included the Medtronic Symplicity system, the Boston Scientific Vessix system, the St. Jude EnligHTN system, and the Covidien OneShot system [21]. However, "off-the-shelf" radiofrequency cardiac ablation catheters not specifically designed for RDN have been very effectively utilized with comparable results and low complication rates compared to proprietary systems (although no direct comparisons have been performed).

Renal arteries with length ≥20 mm and diameter of ≥4 mm are anatomically suitable when considering RDN so as to avoid structural damage to the arterial wall. To identify abnormal vascular anatomies that may interfere with the ablation procedure, renal vascular imaging can be carried out before RDN. For example, pre-ablation renal magnetic resonance angiogram or computerized tomographic angiogram can be performed. Aortogram and/or selective renal angiography at the time of intervention is usually helpful to identify the size

and number of renal arteries, the principal determinants of feasibility of RDN [22]. Renal arteries with visible stenosis, calcification, and atheromatous plaques are also relative contraindications to RDN.

Ultrasound-Based RDN

In order to potentially provide targeted renal sympathetic nerve injury with better precision and fewer complications, the next generation of RDN employed ultrasound-based technologies. The idea was that by generating frictional thermal energy via the interaction of high frequency circumferential ultrasonic waves and the surrounding fluids, improved outcomes may result. The currently available ultrasound ablation technology includes the PARADISE Percutaneous Denervation System (ReCor Medical, Ronkonkoma, NY), the TIVUS system (Cardiosonic, Tel Aviv, Israel), and the Kona Surround Sound system (Kona Medical, Bellevue, WA). Clinical data is not yet available.

Pharmacological Ablation Technology

This novel technique uses a catheter-guided system that aims to locally inject therapeutic agents into the adventitial tissue, eliciting maximal renal nerve ablation without injury to the vessel intima or media. Several systems are being evaluated currently in randomized, sham-procedure controlled trials. To date, this technique has not been evaluated for arrhythmia management.

RDN–Antiarrhythmic Mechanism

The mechanism by which RDN acts as antiarrhythmic is believed to be multifactorial and complex. The fundamental hypothesis behind the antiarrhythmic effect of RDN is supported by prior observations of reduced systemic sympathetic tone following RDN [23]. On a vulnerable cardiac substrate, richly innervated by autonomic nerve fibers, adrenergic activation may act as a trigger, may maintain a source for the maintenance of AF, or both [24]. Animal studies have demonstrated several potential atrial antiarrhythmic effects of RDN including less slowed or heterogeneous conduction, shorter and less dispersed refractoriness, less fibrosis, reduced neurohumoral activation, less sympathetic nerve sprouting, and diminished stellate ganglion activity [25–27]. The mechanism by which RDN improves AF outcome seems to be independent of blood pressure. The SMAC-AF study demonstrated that reducing BP pharmacologically did not translate to any improvement in maintaining sinus rhythm after AF ablation [28]. A group from Greece showed that in 291 hypertensive patients that were randomized to either moxonidine (central sympathetic inhibitor) or placebo, the addition of moxonodine resulted in a significantly lower rate of AF recurrence when compared with placebo, despite no significant difference in blood pressure [29].

Clinical Trials and Published Results

The provocative preclinical observations and the successful antihypertensive trials led to the design and completion of the first-in-man, pilot, randomized controlled trial (RCT) for AF control that was published in 2012 by our group. The trial included a diverse sample of 27 patients with paroxysmal or persistent AF and with resistant hypertension (defined as office blood pressure ≥160/100 mmHg despite at least 3 medications). The results demonstrated that 9 of the 13 patients (69%) treated with PVI with RDN were AF-free at the 12-month post-ablation follow-up examination versus only 4 (29%) of the 14 patients in the PVI-only group (P= 0.033) (Tables 1 and 2) [30•].

In 2014, we published a meta-analysis combining two small RCTs that had enrolled a total of 80 patients. The first study included patients with paroxysmal AF or persistent AF and moderately resistant hypertension (office blood pressure BP ≥140/90 mm Hg and <160/100 mm Hg; n = 48), whereas in the other one all patients had severe resistant hypertension (≥160/100 mm Hg; n = 38). Patients were randomized to PVI or PVI with RDN. Overall, the meta-analysis demonstrated that at 12 months, 26 of the 41 PVI with RDN patients (63%) were AF-free vs 16 of the 39 patients (41%) in the PVI-only group (P = 0.014). In patients with severe hypertension, 11 of the 18 PVI with RDN patients (61%) vs 5 of the 18 PVI-only patients (28%) were AF-free (P= 0.03). However, for moderate hypertension, the differences were less dramatic: 11 of 21 (52%) vs 15 of 23 (65%) when RDN was added (P= 0.19) [31].

The third study was a prospective nonrandomized study from Brazil that enrolled patients with normal renal function who underwent PVI (n = 101), and were compared to those with chronic kidney disease (CKD) patients who underwent either PVI alone (n = 96) or PVI + RDN (n = 39). The primary endpoint was recurrence of AF recorded by 24-h Holter monitoring. The study showed that during a mean follow up of 22 ± 12 months following intervention, the incidence of AF recurrence was higher in CKD patients treated with PVI alone (61%) than in CKD patients treated with PVI + RDN (38%; HR 1.86, 95 % CI 1.14–3.03, P= 0.025) or patients without CKD subjected to PVI (35%; hazard ratio (HR) 2.27, 95 % confidence interval (CI) 1.51–3.42, P < 0.0001) [32].

Table 1 Baseline characteristics of the randomized controlled trials

	ERADICATE-AF	Kiuchi et al	Pokushalov et al	Pokushalov et al
Publication Year	2020	2017	2014	2012
		N. of patients		
RDN + AFA	154	39	39	13
AFA	148	197	41	14
Study design	RCT, single-blind	Prospective, Non-RCT	RCT, double-blind	RCT, double-blind
Age, yrs				
RDN + AFA	59 ± 7	60 ± 14	56 ± 6	57 ± 8
AFA	61 ± 6	60 ± 14	56 ± 6	56 ± 9
Type of AF %				
Paroxysmal	100 (302/302)	100 (236/236)	43.7 (35/80)	33 (9/27)
Persistent	None	None	56.3 (45/80)	67 (18/27)
Diabetes				
RDN + AFA	10.3 (16/154)	36 (14/39)	12.2 (5/41)	7.7 (1/13)
AFA	12.1 (18/148)	39.5 (78/197)	10.2 (4/39)	14.2 (2/14)
SBP, mm Hg				
RDN + AFA	150 ± 9	121 ± 9	163 ± 18	181 ± 7
AFA	151 ± 9	120 ± 9	164 ± 17	178 ± 8
DBP, mm Hg				
RDN + AFA	89 ± 7	79 ± 6	89 ± 11	97 ± 6
AFA	90 ± 7	79.5 ± 6	88 ± 11	96 ± 4
LVEF, %				
RDN + AFA	62 ± 5	66 ± 13	60 ± 4	65 ± 5
AFA	62 ± 5	67 ± 9	61 ± 5	66 ± 4
LA diameter, mm				
RDN + AFA	48 ± 3	39.8 ± 9.4	47 ± 5	49 ± 7
AFA	47 ± 3	35 ± 7.1	47 ± 4	50 ± 6

Values are mean ± SD or % (n/N)

AF = atrial fibrillation; *AFA*= atrial fibrillation ablation; *ERADICATE-AF* = Evaluate Renal Artery Denervation in Addition to Eliminate Atrial Fibrillation; *LA* = left atrial; *LVEF* = left ventricular ejection fraction; *N/R* = not reported; *RCT* = randomized controlled trial; *RDN* = renal sympathetic denervation

∗ Indexed LA volume (ml/m^2)

The largest and most impactful clinical investigation, ERADICATE-AF, enrolled 302 patients in a randomized single-blind trial, and was recently published in JAMA [15]. The ERADICATE-AF trial was an investigator-initiated, multicenter, single-blind, randomized clinical trial conducted at 5 referral centers for catheter ablation of AF in the Russian Federation, Poland, and Germany. All patients needed to have suboptimally controlled hypertension despite taking at least 1 antihypertensive medication, paroxysmal AF, and plans for ablation. Freedom from AF (defined as atrial-fibrillation, flutter, or tachycardia) at 12 months was observed in 84 of 148 (56.5%) of those undergoing PVI alone and in 111 of 154 (72.1%) of those undergoing PVI plus RDN (hazard ratio, 0.57; 95% CI, 0.38 to 0.85; *P*= 0.006) [15].

Of the pre-specified secondary end points, mean systolic blood pressure (from baseline to 12 months) decreased from 151 mm Hg to 147 mm Hg in the PVI-only group and from 150 mm Hg to 135 mm Hg in the RDN group (between-group difference, −13 mm Hg; 95% CI, −15 to −11 mm Hg; *P*< 0.001). Procedural complications occurred in 7 patients (4.7%) in the isolation-only group and 7 (4.5%) of the renal denervation group.

Tables 1 and 2 summarize the published studies of RDN for AF ablation.

In addition to the RCTs, several prospective observational nonrandomized studies and small meta-analyses demonstrated similar consistent findings [32–35]. A recent meta-analysis analyzed data of these cited studies, together with 2 smaller prospective unpublished randomized pilot studies. This meta-analysis including 6 studies (*n*= 725) showed that 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; I^2 = 0%) when compared with AF ablation alone. There

Table 2 Procedure characteristics and outcomes of the randomized studies

	ERADICATE-AF	Kiuchi et al	Pokushalov et al	Pokushalov et al
Type of AF ablation	PVI/CTI	PVI-only	PVI/CTI	PVI/CTI
CTI ablation	16% (49/302)	0%	43% (34/80)	44% (12/27)
RDN RF ablation energy	8-12 W	10 W	8-12 W	8-10 W
RF delivery per lesion	120 s	60 s	60-120 s	120 s
RDN catheter	Irrigated tip catheter	Irrigated tip catheter	Irrigated tip catheter or Symplicity	Irrigated tip catheter
Source of energy for PVI	Cryo	RF	RF	RF
Median RDN lesions per artery	6	N/R	4 (4–6)	4 (4–6)
Follow-up (months)	12	9	12	12
AF monitoring	Holter at 3, 6, 9, and 12 months	Holter at 6 months	Holter at 3, 6, 9, and 12 months	Holter at 3, 6, 9, and 12 months
Renal artery surveillance	None	Doppler US at 6 months	MRA at 6 months	MRA at 6 months
AF recurrence at 12 months				
RDN + AFA	43/154 (28%)	15/39 (38%)	15/41 (37%)	4/14 (29%)
AFA	64/148 (44%)	68/101 (68%)	23/39 (59%)	9/13 (69%)
Periprocedural complications				
RDN + AFA	7/154 (5%)	None	None	None
AFA	7/148 (5%)	None	None	None
Renal artery stenosis at 6 months				
RDN + AFA	NA	None	None	None
AFA	NA	None	None	None

Abbreviations: *AF*= atrial fibrillation; *CTI*= cavo-tricuspid isthmus; *RDN*= renal denervation; *RF*= radiofrequency; *PVI*= pulmonary vein isolation; *AFA*= atrial fibrillation ablation; *NA*= non-applicable; *US*= ultrasound; *MRA*= magnetic resonance angiography

were no significant differences in overall complications between both groups (RR: 1.43; 95% CI: 0.63 to 3.22; $p = 0.40$; $I^2 = 7\%$). Additionally, when compared with baseline, RDN significantly reduced the systolic blood pressure (–12.1 mm Hg; 95% CI: –20.9 to –3.3 mm Hg; $p < 0.007$; $I^2 = 99\%$) and diastolic blood pressure (–5.60 mm Hg; 95% CI: –10.05 to –1.10 mm Hg; $p = 0.01$; $I^2 = 98\%$) during follow-up. Nevertheless, it's important to acknowledge that the ERADICATE-AF study alone had a weight of 43%, and therefore, the results might have been driven by this one study. The prior unpublished studies using proprietary catheters were both not associated with benefit, and one demonstrated potential harm, likely due to high radiofrequency energy delivery.

Current Guidelines and Future Studies

As of now, European and American guidelines have not yet identified RDN as part of standard of care. Both guidelines highlight the importance of hypertension as a risk factor for AF and the importance of optimal post-procedure blood pressure control. Given the very recent publication of ERADICATE-AF, and the supportive meta-analyses, it is conceivable that greater attention will focus on the potential value of RDN as an adjunct to standard ablation of AF.

Several ongoing prospective randomized trials are evaluating the role of RDN in patients indicated for PVI with a history of hypertension (NCT02064764 and NCT02115100). ERADICATE-AF II has recently been awarded funding from the National Institutes of Health (R34 HL153579) and is being launched to study the role of RDN in patients without hypertension, or with medication-controlled hypertension (NCT).

Conclusions

RDN has proven to be a unique, effective and safe interventional therapy for the management of AF. There is strong mechanistic and observational data that the benefits of RDN may be mediated by an antiadrenergic effect on arrhythmic mechanisms central to the development of AF. The fact that RDN is a noncardiac ablation technique with very small risk may further fuel interest as an antiarrhythmic strategy. Future investigation will likely focus on confirming current findings; expanding the population of eligible patients (eg., non-hypertensives, well controlled hypertensives); determining long-term maintenance of effect and therapeutics; and evaluation for use in refractory ventricular tachyarrhythmias for which there is already preliminary positive evidence. After some fits and starts, it now appears that the promise of RDN is being realized.

Declarations

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest Arwa Younis declares no conflict of interest.

Jonathan S. Steinberg reports: Consultant for Medtronic, National Cardiac, Allergan, Atricure, Corfigo, Braveheart, Hillrom; equity in

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