RENAL ARTERY DENERVATION

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Abstract:

Endovascular renal artery denervation, using radiofrequency energy or ultrasound or alcohol for ablation, has demonstrated good efficacy and safety to lower ambulatory blood pressure over a 3 month to 3-year period, proven by sham-controlled, multi-center, randomized controlled trials. While initial subjects were those with resistant hypertension, on multiple antihypertensive medication, subsequent trials have shown impressive results even in medication-naïve patients. At present, this device-based therapy is a promising option that may be applied alone or as a complementary therapy to antihypertensive medication. Individual patient preference should be considered as part of a shared patient-physician decision process, while the procedure establishes its longer-term durability and safety. As a sympathectomy procedure, it is found to be of value in other conditions too, such as cardiac arrhythmias, heart failure and obstructive sleep apnea.

Keywords: Resistant Hypertension, Radiofrequency Ablation, denervation, sympathectomy.

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Renal denervation (RDN) is a process in which catheter-based techniques are used to ablate specific portions of the renal artery nerves with the goal of decreasing sympathetic nerve activity and reducing blood pressure

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1. Indications

2. Resistant Hypertension: Blood pressure (BP) persistently above target despite treatment with 3 different classes of antihypertensive medication at maximum doses, with at least one diuretic; or BP that is successfully controlled using at least 4 medications. With ACC/AHA 2017 BP criteria of ≥130/80 for defining HTN, anywhere between 32-46% of adults are hypertensives. Among adults with hypertension, various studies have estimated the prevalence of resistant hypertension to range between 12% and 18%.
3. Arrhythmias: Atrial fibrillation (AF): In the ERADICATE-AF trial among patients with paroxysmal AF and hypertension, RDN added to catheter ablation for pulmonary vein isolation, significantly increased the likelihood of freedom from AF at 12 months when compared with catheter ablation alone. For refractory ventricular tachycardia (VT) including VT storm, RDN demonstrates the potential benefit when VT recurs after radiofrequency ablation and cervical sympathetic denervation.
4. Obstructive Sleep Apnea (OSA): RDN demonstrated sustained reduction in office and ambulatory BP, and there was a significant decrease in OSA severity measured by apnea/hypopnea index.
5. Congestive Cardiac Failure (CCF): RDN decreased left ventricular mass index, and improved diastolic function, reduced interventricular septum thickness, decreased end-systolic volume, and improved ejection fraction. REACH-Pilot study demonstrated improvements in both symptoms and exercise capacity in patients with chronic systolic heart failure 6 months after RDN.
6. Other Comorbidities: Benefit of RDN was shown in pulmonary vascular remodeling and pulmonary hypertension,insulin resistance, gestational hypertension,anxiety, depression, and self-assessed physical and mental status.

Applied Anatomy of Renal Sympathetic System
Studies have shown that 90% of renal artery nerves are within 6-7 mm of the artery lumen. In addition, while proximal and middle segments of the renal artery have a higher nerve density, nerves become closer to the lumen as the artery courses distally (90% of nerves within 3 mm after the bifurcation)[1].
Physiology of Renal Sympathetic System[1]:
The renal sympathetic nervous system consists of both the afferent and efferent sympathetic nerve fibers. Renal afferent sensory fibers are activated by various stimuli such as renal ischemia, hypoxia and oxidative stress through baroreceptors and chemoreceptors, resulting in increased stimulation of the hypothalamus leading to increased sympathetic outflow to the kidneys, and other organs such as the heart and peripheral vasculature. Activation of the efferent sympathetic nerves results in renal arteriolar vasoconstriction with reduced renal blood flow, increased renin secretion and subsequent activation of the angiotensin-aldosterone activity, and increased sodium and water absorption resulting in increased intravascular volume and maintenance of systemic hypertension.

Renal Sympathetic Denervation (RSD)- Initial Surgical Procedure Results: Lack of effective drugs for resistant hypertension led to exploring surgical subdiaphragmatic splanchnicectomy as a therapeutic intervention. The splanchnic nerve and thoracic dorsal sympathetic chain were resected to interrupt sympathetic outflow, leading to lowering BP and systemic vascular resistance[1]. While encouraging acute and long-term reduction in BP as well as improvement in survival, was seen, there were side effects such as postural-hypotension, hyperhidrosis, sensory and sexual dysfunction, depression, with poor tolerance of the invasive procedure; hence, surgical approach was largely abandoned after the advent of new antihypertensive medications. But need for alternative therapeutic strategies to control adverse cardiovascular effects of resistant hypertension, led to the development of catheter-based interventional approach to RDN.
Catheter-Based Approach to RDN[1]:
This procedure results in BP reduction in resistant HTN without significant adverse effects. Reduction in endogenous homeostatic signaling between brain and the kidney from the disruption of the vascular adventitia renal efferent and afferent sympathetic nerves is presumed to be reason for this benefit.

Current Technologies of RDN: These include the use of catheter-directed radiofrequency ablation, ultrasonic ablation therapy, and pharmacological ablation that is locally delivered through infusion catheters[1].
RF Catheter Ablation: Renal arteries with length 20 mm and a diameter of 4 mm are anatomically suitable when considering renal denervation so as to avoid structural damage to the arterial wall. However, renal arteries with visible stenosis, calcification and atheromatous plaques present a relative contraindication to renal denervation. RF renal nerve ablation involves accessing renal artery with an endovascular catheter via femoral artery approach using a 6F or 8F guide. The catheter is positioned toward the distal renal artery and multiple 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[1]. The circumferential fashion ensures the entire circumference of the artery has been treated.

Recommendations for Peri-procedural Pharmacotherapy: An expert consensus document from the European Society of Cardiology recommends the use of antiplatelet therapy (acetylsalicylic acid 250 mg IV.) during and for at least 4 weeks postprocedure (75- 100 mg/day p.o.) to avoid formation of thrombus as a result of transient deendothelialization from ablation therapy[1].

Results of Radiofrequency Catheter Ablation-based Studies[1]: Encouraging results from the initial studies led to the approval of catheter-directed radiofrequency ablation technologies which were subsequently used for prospective clinical trials world-over. These are the Medtronic's Symplicity system, St. Jude's EnligHTN system, Boston Scientific's Vessix's V2 system.

Following promising results of SYMPLICITY HTN-1 trial, that was open-label and lacked control group, SYMPLICITY HTN-2 was conducted as randomized, single-blind trial with single electrode (SIMPLICITY Flex) catheter. This showed BP reduction of 33/14 mm Hg in RDN group at 3 years, but only 11/7 mm Hg in 24-hour ambulatory BP monitoring (ABPM), which could be due to study bias. SYMPLICITY HTN-3 trial was rigorously designed as a prospective, randomized, sham-controlled, single blind trial that required screening with 24-hour ABPM, randomized 535 subjects in a 2:1 fashion to renal denervation or a sham procedure, and showed no difference in BP reduction between the two groups[2]. Preclinical study has demonstrated a significant reduction in renal norepinephrine level only where ablation involved all 4 quadrants, reached a depth of 9.1 mm, and affected 50% of the nerves[1]. Since all these trials used single tip electrode catheter with lesser distal reach and depth of non-circumferential ablation, those criteria may not have been fulfilled in many patients. Inadequate renal denervation resulting in an ineffective procedure may explain the result of the SYMPLICITY HTN-3 trial.

This led to development of the second generation SymplicitySpyral catheter, with 4-electrode catheter design, capable of causing circumferential ablation from a single application, reaching even distal branches, so as to achieve effective denervation. Both SPYRAL HTN-OFF MED (in untreated HTN patients) and SPYRAL HTN-ON MED (patients on 1-3 drugs) were randomized sham-controlled multicenter trials done with this catheter with ablation of both main renal artery and branch arteries. Latter showed at 6months, 24-hour ABPM (7.0/4.3 mm Hg) and office blood pressure (6.6/4.2 mm Hg) were significantly reduced in the renal denervation group compared with sham-control group, without serious adverse effects. Long term results of the latter study continued to show durable, clinically significant blood pressure reductions through 3 years (2022)[3].

Similar positive results were noted in EnligHTN 1 and EnligHTN III trials using ablation with another company's multielectrode catheter that allowed simultaneous delivery of ablation therapy to 4 electrode sites showed sustained BP reduction over 6-24 months, with no reported device or procedure related adverse events affecting the renal arteries or function[1].

REDUCE-HTN trial, used an over the wire balloon catheter from yet another company, that had electrodes and thermistors mounted on the exterior of the balloon, inflation of which allowed for simultaneous delivery of RF ablation energy in small renal arterial branches with diameter of 3.0 mm, showed sustained reduction in BP of resistance hypertension patients up to 2 years, and with a low-risk safety profile for appropriately selected patients [1].

Ultrasound (US)-Based Renal Denervation Therapy: Using PARADISE US ablation device consisting of a balloon catheter with a cylindrical transducer that provides circumferential rings of ultrasonic ablative thermal energy of 1-6 mm in depth, while simultaneously circulating a cooling fluid in the balloon that protects the endothelial wall from frictional generated heat, REDUCE HTN trial showed its safety and the efficacy[1]. Six-month results from the RADIANCE-HTN SOLO trial, a randomized, blinded, sham-controlled trial, showed sustained reduction in day time ambulatory systolic BP to a greater extent than sham (18.1 vs 15.6 mm Hg, P = 0.024), respectively, with no major adverse events in either group[1]. Similar sustained BP reductions over 6 months, without significant adverse effects were also seen with using other ultrasound catheters, without balloon cooling[1].

RF Versus US Energy for RDN: RADIOSOUND-HTN trial was a single center trial to assess the efficacy of RF current using Simplicity Spyral catheter for main renal arteries versus main+branch vessels, both being compared with endovascular US energy ablation of main renal arteries. In 120 patients, at 3 months, daytime ASBP reduction was similar with US energy in main renal arteries and RF ablation of both main+branch arteries, with lesser efficacy when only RF ablation of main renals was done[4].

External ultrasound imaging guidance using Doppler to deliver focused US

energy to the renal nerves, WAVE I and WAVE II trials showed significant sustained benefit in BP reduction over 6-month period. However, the WAVE IV trial, which was a phase II randomized,

sham-controlled, double-blinded trial of RDN in individuals with uncontrolled hypertension, was prematurely stopped because the data did not prove that antihypertensive efficacy of externally delivered focused ultrasound for RDN was greater than the sham effect[1].

Pharmacological Ablation Technology:
Studies using catheter -guided pharmacological ablation technology that aim to locally inject therapeutic agents into the adventitial tissue are underway (TARGET BP I and the TARGET BP OFF-MED with promising preclinical results[1].
Complications of RDN: While potential complications of the procedure include arterial stenosis, thrombosis and dissection, reassuringly, there were limited adverse events, and no instances of renal artery stenosis. The 3-year safety data of the entire Global Symplicity registry demonstrated a low long-term incidence of adverse events (cardiovascular death 1.9%, hospitalization for hypertensive crisis 4.4%, new onset end stage renal disease 1.9%, and new renal artery stenosis 0.2%)[1].
Present Position of Various Authoritative Bodies on RDN: US Food and Drug Administration (FDA) advisory panel on 05/12/2018 concluded that reduction in medication burden was clinically meaningful but need exists for accruing data on patients' preferences and continued focus on safety in post-surveillance data[5]. European Society of Cardiology-European Society of Hypertension (ESC-ESH) 2018 guideline for the management of arterial hypertension mandated that routine use of any device therapy for hypertension was not recommended outside the context of clinical trials (class II recommendation, grade B level of evidence)[6].Joint UK societies' 2019 consensus statement on renal denervation stated that there is insufficient data at present to suggest that RDN should be considered routine standard of care in the management of hypertension in adults and that additional clinical trials data are required to establish durability and safety[7].
The Asia Renal Denervation Consortium consensus conference 2019, in contrast to the above, recommended that, RDN should not be considered a therapy of last resort but as an initial therapy option that may be applied alone or as a complementary therapy to antihypertensive medication. These were based on considerations that in Asia, the impact of hypertension on cardiovascular disease is greater, and the rate of uncontrolled hypertension is higher than in Western countries. Therapy should not necessarily be restricted to clinical trials or centers of excellence if proper procedural training and internal cooperation between referring physicians, hypertension specialists, and operators has been achieved[8].

Cost-Effectiveness Analysis: When analyzed in the Symplicity HTN-2 trial, median survival was 18.4 years for RDN compared to 17.1 years for standard of care and the incremental cost-effectiveness ratio was cost-saving to $31,460 per quality-adjusted life-year[1].

2. Conclusions

Renal denervation is a promising therapeutic intervention for catheter based sympathectomy, having undergone many improvisations and has been well-tested in sham-controlled studies to show its efficacy and safety in the short and intermediate-term, for managing patients with resistant hypertension, as well as other conditions with chronically elevated sympathetic activity. For select persons with hypertension who experience multidrug intolerance or who are not willing to take medications to achieve adequate BP control, renal artery denervation may be a valuable therapy.

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