Renal Sympathetic Denervation: A Comprehensive Review

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Abstract: In 2017, the American College of Cardiology and American Heart Association released its updated blood pressure guidelines, redefining hypertension to be any systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥80 mm Hg. Among United States adults, these new parameters increased the prevalence of hypertension from 72.2 million (31.9%) to 103.3 million (45.6%) adults and decreased the rate of medication-controlled hypertension from 53.4% to 39% with the prevalence of resistant hypertension ranging from 12% to 18%. Results of the pivotal SPRINT trial showed that more intensive blood pressure control in diabetic patients decreased both cardiovascular events and all-cause mortality. However, even with ideal goals in mind, compliance remains an issue due to multiple causes, and approximately half of study participants had stopped taking their antihypertensive drug within a year. Renal sympathetic denervation 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. Several studies using renal artery denervation have already shown benefit in patients with resistant hypertension, and now newer trials are beginning to focus on those with

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stage II hypertension as an additional potential treatment population. This review will seek to summarize the current evidence surrounding renal artery denervation and discuss some of its future trials, current issues, and potential roles both in hypertension and other comorbidities. (Curr Probl Cardiol 2021;46:100598.)

Introduction

In 2017, the American College of Cardiology and American Heart Association (ACC/AHA) released its updated blood pressure guidelines, redefining hypertension to be any systolic blood pressure ≥130 or diastolic blood pressure ≥80; among United States adults, these new parameters increased the prevalence of hypertension from 72.2 million (31.9%) to 103.3 million (45.6%) adults and decreased the rate of medication-controlled hypertension from 53.4% to 39.0%.[1] The former mark for hypertension, set by the JNC 7 guidelines at a systolic blood pressure ≥140 or diastolic blood pressure ≥90, is now the threshold for stage II hypertension per the ACC/AHA guideline.[1]

Resistant hypertension is now widely defined as blood pressure persistently above target despite treatment with 3 different classes of antihypertensive medication at maximum doses, with at least one diuretic; alternatively, it can also refer to blood pressure that is successfully controlled using at least 4 medications.[2] Among adults with hypertension, various studies have estimated the prevalence of resistant hypertension to range between 12% and 18%.[3,4] These patients have a higher risk of cardiovascular events (death, myocardial infarction, heart failure, stroke, and chronic kidney disease) when compared to those with controlled hypertension.[5]

Results of the SPRINT trial suggests that in hypertensive patients without diabetes more intensive blood pressure control (goal systolic blood pressure <120 mm Hg vs 140 mm Hg) decreases both cardiovascular events and all-cause mortality.[6] However, even with ideal goals in mind, compliance remains an issue. In one large-sample longitudinal database study (n = 4783), roughly half of participants had stopped taking their antihypertensive drug within a year.[7] The Center for Diseases Control and Prevention determined that, in 2014, around 26.3% (4.9 million) of Medicare Part D beneficiaries were not adherent to their blood pressure regimens.[8] Patients with high adherence (≥80%) to antihypertensive therapy have a lower relative risk of developing complications such as heart

failure (11%), coronary artery disease (10%), and cerebrovascular disease (22%).[9-11] There are multiple causes of medication nonadherence; some of these factors may include lack of healthcare or concern with cost, communication barriers between healthcare workers and elderly patients or non-English speakers, and motivational barriers for those with poor understanding of their illness or fear of adverse medication effects.[12]

Aside from the issues regarding medication efficacy or patient compliance, hypertension is an expensive disease. According to the AHA, the average patient with hypertension created an extra $2000 dollars annually in healthcare costs between 2003 and 2014; during this same period, annual healthcare expenditures associated with hypertension averaged around $131 billion.[13] America now has vast numbers needing treatment with an increasingly aging population, high rates of stress and obesity, excessive dietary sodium and alcohol intake, and many with a sedentary lifestyle. Treatment often requires both medications and behavioral changes, which are notoriously difficult.

When considering a disease that continues to be very difficult to manage, perhaps it is time to consider alternative treatment approaches. Renal denervation is a process in which catheter-based radiofrequency, ultrasound, and now chemical-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. Several studies using renal artery denervation have already shown benefit in patients with resistant hypertension, and now newer trials are beginning to focus on those with stage II hypertension as an additional potential treatment population. This review will seek to summarize the current evidence surrounding renal artery denervation and discuss some of its future trials, current issues, and potential roles both in hypertension and other comorbidities.

Renal Artery Sympathetic Nerve Distribution

Much of the current anatomical knowledge surrounding renal artery denervation is based on autopsy studies that produce histological samples of renal arteries and surrounding nerves. Atherton et al[14] first postulated that more than 90% of renal artery nerves are within 2 mm of the artery lumen; however, the study only assessed for nerves up to 2.5 mm from the lumen. Sakakura et al[15] used a broader study design that included samples from both hypertensive and nonhypertensive patients, a more thorough inspection for surrounding nerves, and immunohistochemistry to differentiate between afferent and efferent nerves. Results showed similar anatomy between the 2 groups and found that 90% of nerves lie

within 6-7 mm of the renal arterial lumen; additionally, 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).[15]

Initial renal denervation trials focused on ablation in the main renal artery, but newer data indicate that postbifurcation vessels may be the better therapeutic targets. Mompeo et al[16] used surgical microscopes to dissect renal nerves and arteries in 12 human cadavers, finding that more of the neural network was found after the arterial bifurcation and suggesting that renal artery denervation needed to be targeting these areas. A unilateral renal denervation study in pigs found a more significant decrease in renal norepinephrine when ablating postbifurcation vessels (74%) as compared to the distal main artery (45%) or ostium (12%).[17] Although newer trials are now studying ablation of postbifurcation vessels, the safety of this remains less clear in humans.

Physiology of Renal Sympathetic Control

The renal sympathetic nervous system consists of both the afferent and efferent sympathetic nerve fibers that play an essential role in the pathophysiology of hypertension. 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.[18,19]

In addition, various stimuli such as renal ischemia, hypoxia and oxidative stress activate the renal afferent sensory fibers 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. This sympathetic outflow results in increased systemic vascular resistance and hypertension.[20,21]

The increased renal sympathetic outflow can be quantified from the clinical method known as "norepinephrine spillover," a technique that involves measuring organ specific outward flux of endogenous norepinephrine.[22] Plasma concentration of norepinephrine and the rate of release of norepinephrine into plasma have been shown to be higher in hypertensive patients than in normal individuals.[22] By decreasing sympathetic activity at the level of the renal sympathetic nerves, as with ablation in renal denervation procedures, Schlaich et al[23] demonstrated a marked reduction in renal norepinephrine spillover from both kidneys (48% from the left kidney and 75% from the right kidney), marked reduction in renin activity, and a

progressive and sustained reduction in systemic blood pressure from 161/107 mm Hg at baseline to 127/81 mm Hg at 12 months. In addition, the whole-body norepinephrine spillover was reduced by 42%.

Renal Sympathetic Denervation – Historical Perspective

Prior to the widespread availability of pharmacological treatment for resistant hypertension, and the resulting poor outcomes of malignant 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 lowering of blood pressure, and systemic vascular resistance.[24]

The benefit of splanchnicectomy was shown in surgical series of 1,266 patient followed for 5 years in a large nonrandomized clinical trial.[25] Surgery consisted of thoracolumbar splanchnicectomy through the beds of the 12th or the 11th and 12th ribs. The sympathetic trunks were removed from the first or second lumbar vertebra, and the great splanchnic nerves were removed from the celiac ganglion to the midthoracic level. The 5-year mortality rate for those treated surgically (n = 1,266) versus those treated medically (n = 467) were 19% and 54%, respectively.[25] There was also sustained blood pressure control in a significant number of patients. However, the nonselective nature of the side effects such as postural-hypotension, hyperhidrosis, sensory and sexual dysfunction, depression, and the invasiveness of the procedure were poorly tolerated, therefore the surgical approach was largely abandoned after the advent of new antihypertensive medications.

Hypertension control however remains poor, and its associated cardiovascular effects remain high, hence the need for alternative therapeutic strategies has led to the development of catheter-based interventional approach to renal sympathetic denervation (RSD).

Catheter-Based Approach to Renal Sympathetic Denervation

Catheter-based endovascular RSD gained traction and validity with the publication of its safety and efficacy in substantially reducing blood pressure in treatment-resistant hypertensive patients,[26] and sustained reduction in blood pressure out to 2 or more years without significant adverse events.[27] The reduction in endogenous homeostatic signaling between

the brain and the kidney from the disruption of the vascular adventitia renal efferent and afferent sympathetic nerves is thought to result in the reduction of this systolic blood pressure.

The current technologies of percutaneous RSD include the use of catheter-directed radiofrequency ablation, ultrasonic ablation therapy, and pharmacological ablation that is locally delivered through infusion catheters.[28]

Catheter-Directed Radiofrequency Ablation

Catheter-directed renal denervation using radiofrequency ablation was pioneered by earlier studies done by Krum et al.[29] In this 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. There was also substantial reduction in renal norepinephrine spillover at 15 to 30 days postprocedure.[29]

Radiofrequency renal nerve ablation involves floating an endovascular catheter into the renal artery via a 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.[30] The circumferential fashion ensures the entire circumference of the artery has been treated. Approximately 5 to 6 applications of ablation therapy 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,[31] which are potential complications. Other complications associated with the procedure include renal artery dissection during stent implantation.[32]

An expert consensus document from the European Society of Cardiology recommends the use of antiplatelet therapy (acetylsalicylic acid 250 mg i.v.) during and for at least 4 weeks postprocedure (75-100 mg/day p.o.) to avoid formation and propagation of a thrombus as a result of transient deendothelialization from ablation therapy.[33] Renal arteries with length $\geq$20 mm and a diameter of $\geq$4 mm are anatomically suitable when considering renal denervation so as to avoid structural damage to the arterial wall.[32,33] However, renal arteries with visible stenosis, calcification and atheromatous plaques present a relative contraindication to renal denervation.[33]

Result from the pioneer study described earlier led to the approval of 4 catheter-directed radiofrequency ablation technologies which were subsequently used for prospective clinical trials over the world (Table 1). These are the Medtronic's Symplicity system, Boston Scientific's Vessix's V2 system, St. Jude's EnligHTN system and Covidien's One-Shot system.[32]

The Medtronic's Symplicity Renal Denervation device (Symplicity Renal Denervation System; Medtronic, Inc., Mountain View, CA) was used in the SYMPLICITY HTN trials. The SYMPLICITY HTN-1 trial was an open-label study that enrolled 153 patients with resistant hypertension, and initially followed for 24 months,[27] and subsequently 36 months.[34] Patients with at least a systolic blood pressure of 160 mm Hg, who were taking at least 3 antihypertensive drugs, including a diuretic, at the optimum doses were eligible for the study. A total of 88 patients had complete data at 36 months and reduction in systolic (−32·0 mm Hg, 95% confidence interval −35·7 to −28·2) and diastolic (−14·4 mm Hg, −16·9 to −11·9) blood pressure were progressively sustained, with drops of 10 mm Hg or more in systolic blood pressure seen in 69% of patients at 1 month, 81% at 6 months, 85% at 12 months, 83% at 24 months, and 93% at 36 months.[34] The results of the SYMPLICITY HTN-1 trial was however confounded by lack of a control group, the open-label design, and a lack of mandatory assessment of 24-hour ambulatory blood pressure.

The SYMPLICITY HTN-2 trial was designed as a randomized controlled trial, and randomized 106 patients to either renal artery denervation or medical therapy alone after 2 weeks of compliance with antihypertensive medications.[35] There were 70 patients with long-term follow up data. They consist of 40 patients from the original renal denervation group who had follow up for 36-month postrandomization, and 30 control subjects that crossed over to the renal denervation group at 6-month postrandomization and had follow up for 30 months. The mean office blood pressure change at 30 months among all patients who underwent renal denervation was −34/−13 mm Hg, and was −33/−14 mm Hg in the initial renal denervation group at 36 months.[35] The 24-hour ambulatory blood pressure reduction was 11/7 ± 15/11 mm Hg, a smaller reduction compared to office blood pressure, raising the possibility of white-coat hypertension, but could also be related to study design and bias effect.[36] The study personnel and subjects were not blinded to study group allocation, and the control group did not undergo a sham procedure.

TABLE 1. Landmark renal denervation trials

				Outcomes				
				Mean reduction in office BP (mm Hg)		Mean reduction in 24-hr ABP (mm Hg)		
Study	Study design	Device	Sample size	6 months	Longest follow-up; (pts; mths)	6 months	Longest follow-up; (pts; mths)	*P*-value
Symplicity HTN-1[34]	Open-labeled	Symplicity Flex	153	−22/−10.2	−32/−14.4 (88;36)			Significant
Symplicity HTN-2[35]	RCT	Symplicity Flex	106	−28.3/−10.4	−32.7/−13.6 (40;36)			Significant
Symplicity HTN-3[38,39]	RCT, single-blinded, sham-controlled	Symplicity Flex	535	−15.5/−6.6 Sham group −11.7/−5	−18.9/−7.8 (319;12) Sham group −21.4/−8.2 (48;12)	−6.4/−3.8 Sham group −4.8/−4	−7.6/−4.7 (247;12) Sham group −6.1/−2.9 (20;12)	Nonsignificant
DENERHTN[42]	RCT, open-labeled, blinded endpoints	Symplicity Flex	106	−15.1/−9.1 Control group −9.5/−6.0		−15.4/−9.7 Control group −9.5/−6.6		Significant
SPYRAL HTN-OFF MED[46]	RCT, sham-controlled	Symplicity Spyral; Symplicity G3	80	−10/−5.3 (3 months) Sham group -2-3/−0.3		−5.5/−4.8 (3 months) Sham group −0.5/−0.4		Significant
SPYRAL HTN-ON MED[47]	RCT, single-blinded, sham-controlled	Symplicity Spyral; Symplicity G3	80	−6.6/−4.2 Sham group −2.6/−1.7		−7/−4.3 Sham group −1.6/−1.9		Significant
EnligHTN III[50]	Prospective cohort, nonrandomized	EnligHTN multielectrode catheter	39	−25/−7	−27/−9 (35;24)	−9/−3	−13/−5 (33;24)	Significant
REDUCE-HTN[51]	Prospective cohort	Vessix's V2	146	−24.5/−10.3	−28/−10.3 (124;24)		−8.5/−5.4 (86;12)	Significant

(*continued on next page*)

TABLE 1. (*continued*)

				Outcomes		
				Mean reduction in office BP (mm Hg)	Mean reduction in 24-hr ABP (mm Hg)	
RADIANCE-HTN SOLO[58]	RCT, single-blinded, sham-controlled,	Paradise multielectrode ultrasonic catheter	146	−18.2/−10.1 Sham group −15.9/−9.5	−16.5/−9.7 Sham group −14.9/−9.4	Significant ONLY for ABP
TIVUS I & II[61]	Prospective, open-label, nonrandomized	TIVUS ultrasonic catheter system	39	−30.6/−14.1	−6.8/−4.5	Significant
WAVE IV[63]	RCT, double-blinded Sham-controlled,	Kona Surround externally-applied Sound system	81	−12.8/−5.1 Sham group −23/−8.9	−7.1/−5.0 Sham group −5.1/−4.5	Nonsignificant

ABP, ambulatory blood pressure; BP, blood pressure; Mths, months; Pts, patients; RCT, randomized control trial.

To overcome some of the limitations of the earlier Symplicity trials, SYMPLICITY HTN-3 trial was rigorously designed as a prospective, randomized, sham-controlled, single−blind trial that randomize subjects in a 2:1 fashion to renal denervation or a sham procedure, and required screening with 24-hour ambulatory blood pressure monitoring to exclude subjects with white-coat hypertension.[37] A total of 535 patients were randomized as above. At 6 months, the mean change in systolic blood pressure in the renal denervation group was -14.13 ± 23.93 mm Hg, and -11.74 ± 25.94 mm Hg in the sham-procedure group (for a difference of -2.39 mm Hg, $P = 0.26$ for superiority with a margin of 5 mm Hg); and a mean change in 24-hour ambulatory systolic blood pressure of -6.75 ± 15.11 mm Hg in the renal denervation group and -4.79 ± 17.25 mm Hg in the sham-procedure group (for a difference of -1.96 mm Hg, $P = 0.98$ for superiority with a margin of 2 mm Hg).[38] At 6 months, there was no significant reduction of systolic blood pressure after renal denervation as compared with a sham procedure in patients with resistant hypertension. The 12 month follow up data showed no further reduction in office and ambulatory blood pressures.[39]

Following extensive posthoc analysis, several identified technical and procedural pitfalls were thought to play a role in the failure of the Symplicity HTN3 trial.[40,41] The study required only 2 weeks of antihypertensive regimen prior to enrolment, and 39% underwent medication changes after inclusion and randomization, with one-third of these patients having at least 2 medications changed, challenging the notion that patients were on maximally tolerated antihypertensive medications prior to enrolment, and if 2 weeks was sufficient duration enough to achieve maximal blood pressure on antihypertensive medication.[36,41] Interestingly, there was a marked decrease in systolic pressure (-21.9 mm Hg) among Black subjects receiving a vasodilator in the sham control group that was not observed in other subgroups,[41] raising the possibility of change in medication adherence during the study, at level much higher than preenrolment.

The issue of adherence was addressed in a well-designed DENERHTN trial,[42] an open-label randomized controlled trial with a blinded end point conducted in truly drug-resistant hypertensive patients using the Symplicity Flex catheter. Patients were randomized 1:1 to receive either standardized stepped-care antihypertensive treatment alone or standardized stepped-care antihypertensive treatment and renal denervation. Both groups showed a reduction in daytime ambulatory systolic blood pressure, with a greater significant reduction in the renal denervation group (-15.8 mm Hg vs -9.9 mm Hg).[42] The small in-between group

difference however failed to allay fears that renal denervation may not improve blood pressure as much as originally thought.

The first-generation Medtronic Symplicity Flex catheter was used in the SYMPLICITY trials. The catheter uses a single monopolar electrode attached to its tip. This catheter tip electrode need maneuvering into specific ablation position, and it is operator dependent. Question regarding limited operator's experience in the SYMPLICITY HTN-3 has been raised. The physicians involved were among the first to perform renal denervation in the United States, and subgroup analysis revealed approximately 35 operators performed only one procedure.[36] In addition, the Symplicity Flex catheter average depth of ablation is 4 mm deep which will theoretically miss about 30% of renal artery nerves because the nerves can be distributed as deep as 10 mm from the vessel lumen and only approximately 75% of renal nerves are located within 4.67 mm of the lumen proximally and 3.24 mm distally.[15,36] The Symplicity Flex catheter also limits ablation to the main renal artery and not the branch arteries. It is worth noting that combined ablation of the main renal artery and branches improve blood pressure-lowering efficacy of renal denervation.[43]

The Symplicity Flex catheter also has limitation in achieving optimal circumferential ablation. Operators pull and rotate the catheter to perform circumferential ablation, however approximately 75% of patients in the SYMPLICITY HTN-3 study did not receive the recommended 4-quadrant circumferential ablation in at least one artery.[41] Comparison of propensity score matched sham cohorts showed progressive reduction in systolic blood pressure in those with 4-quadrant ablation.[41]

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.[44] Therefore, the circumferential and depth limitation of the Symplicity Flex catheter may have resulted in inadequate renal denervation resulting in an ineffective procedure that may explain the result of the SYMPLICITY HTN-3 trial.

These challenges were addressed with the development of the second-generation Symplicity Spyral catheter. It is a 4-electrode catheter design that is capable of achieving 4 times the number of ablations of the single electrode Symplicity Flex catheter, including branch arteries as small as 3 mm, resulting in more effective and consistent denervation and greater antihypertensive response.[40] The Medtronic second-generation Symplicity Spyral catheter was used in the positive SPYRAL HTN Global Clinical Trial Program,[45] a trial specifically designed to avoid the pitfalls of

the SYMPLICITY HTN-3 trial. The trial consists of 2 parts; The SPYRAL HTN-OFF MED[46] and the SPYRAL HTN-ON MED trials.[47]

The SPYRAL HTN-OFF MED was a proof-of-concept multicenter, randomized, sham-controlled renal artery denervation study in patients with untreated hypertension and an office systolic blood pressure ≥150 mm Hg and ≤180 mm Hg. Renal denervation was performed using the Symplicity Spyral multielectrode catheter or the Symplicity G3 catheter, and ablation was done in both main renal artery and branch arteries. At 3 months, renal denervation resulted in greater reduction in both office (−10/−5.3 mm Hg) and 24-hour ambulatory blood pressure (−5.0/−4.4 mm Hg) compared to sham-control group that showed no significant change in blood pressure.[46] There were no reported safety concerns.

The SPYRAL HTN-ON MED was also a randomized, sham-controlled, single blind trial in patients with uncontrolled hypertension on 1-3 antihypertensive medications. The same protocol was followed as the SPYRAL HTN-OFF MED trial. The patients underwent drug screening to assess medication adherence using urine and plasma analysis. At 6 months, 24-hour ambulatory (−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 the sham-control group.[47] The between group difference was −7.4/−4.1 mm Hg and −6.8/−3.5 mm Hg for the 24-hour ambulatory and office blood pressures respectively. There was no significant change in renal function and no reports of renal artery stenosis in either group.[47] These studies conducted with the redesigned Symplicity Spyral catheter, and ablation of both the main renal arteries and branch arteries are encouraging and support the concept that, if done properly, renal denervation reduced arterial blood pressure in patients with resistant hypertension.

The EnligHTN Multielectrode Renal Denervation System (St. Jude Medical Inc., St Paul, Minnesota) is a multielectrode design with a predefined geometric orientation that allows simultaneous delivery of ablation therapy to 4 electrode sites along the endoluminal surface of renal artery, with a benefit of reducing total ablation time.[48] The safety and efficacy of this device was reported in the first-in-human, prospective, multicenter, nonrandomized EnligHTN 1 trial.[49] There was a significant reduction in the office blood pressure from baseline to 1, 3, and 6 months by −28/10, −27/10 and −26/10 mm Hg, respectively, and with no acute renal artery injury or other serious vascular complications.[49] Sustained reduction in blood pressure up to 24 months was reported in the EnligHTN III trial, with no reported device or procedure related adverse events affecting the renal arteries or function.[50]

The Boston Scientific's Vessix's V2 Renal Denervation System (Vessix Vascular Inc., Laguna Hills, California and Boston Scientific Inc., Minneapolis, MN) is an over the wire balloon catheter that has electrodes and thermistors mounted on the exterior of the balloon. The balloon catheter can be maneuvered into small renal arterial branches with diameter of 3.0 mm. Inflation of the balloon allows for simultaneous delivery of radiofrequency ablation energy resulting in disruption of the renal nerves located in the adventitia of renal arteries. The safety and efficacy of this RSD system was evaluated in the REDUCE-HTN trial[51] which showed sustained reduction in blood pressure of patients with resistance hypertension up to 2 years, and with a low risk safety profile for appropriately selected patients.

The OneShot Renal Denervation System (Covidien, Dublin, Ireland) is an over-the-wire balloon-based irrigated catheter technology with a surface polar electrode that delivers a single radiofrequency treatment per artery. The catheter reduces radiofrequency ablation-induced endothelial injury through a constant saline irrigation system delivered to the electrodes through side holes, and the monopolar electrode delivers targeted and controlled ablation energy that avoids the potential of circumferential injury with other catheters.[32,36] Results from the Rapid Renal Sympathetic Denervation for Resistant Hypertension Using the OneShot Ablation System Study (RAPID) demonstrated safe delivery of radiofrequency energy and sustained efficacy of office and 24-hour ambulatory blood pressure control for 6 months and up to 12 months.[52] However, the OneShot program was eliminated in 2014 by Covidien, citing a slower than expected development in the renal artery denervation market.[36]

Other radiofrequency ablation catheters under investigation include the GL-06E15WA ablator and GL-6W ablation catheter (Shanghai Golden Leaf Medtech Company, Shanghai, China), 6-point reticular electrodes ablation catheter that supplies 360° circular ablation without affecting renal artery blood flow. A pilot study was conducted with 15 patients who were followed up for 6 months showed reduction in office systolic (-11.5 ± 9.9 mm Hg), diastolic (-6.9 ± 4.8 mm Hg), mean 24-hour ambulatory systolic (-7.5 ± 7.7 mm Hg) and mean 24-hour ambulatory diastolic (-3.3 ± 4.7 mm Hg) blood pressures compared to baseline values.[53] The AUSHAM-RDN-01 trial (Australian SHAM Controlled Clinical Trial of Renal DeNervation in Patients With Resistant Hypertension)[54] and the SYNAPTIC trial (A Prospective, Multi-centers, Randomized, Controlled Study of Assessing the Safety and Efficacy of Sterile Irrigated Deflectable Ablation Catheter Used in Renal Artery in

Primary Hypertension)[55] will be completed in April 2020 and September 2020 respectively.

Ultrasound-Based Renal Denervation Therapy

The ultrasonic RSD catheters was developed to provide targeted renal sympathetic nerve injury with better precision by generating frictional thermal energy through the interaction of high frequency circumferentially emitted ultrasonic waves emitted and the surrounding fluids. The currently available ultrasound ablation technology includes include 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).

The PARADISE Percutaneous Renal Denervation System: The paradise endovascular ultrasound ablation catheter (ReCor Medical, Ronkonkoma, NY) consists of a 6F compatible balloon catheter with a self-centering cylindrical transducer that provides circumferential rings of ultrasonic ablative thermal energy of 1-6 mm in depth to disrupt the renal artery sympathetic innervation, while simultaneously circulating a cooling fluid in the balloon that protects the endothelial wall from frictional generated heat.

The safety and the efficacy of the PARADISE ultrasound ablation device (ReCor Medical, Palo Alto, CA) was first evaluated in the REDUCE HTN trial[56] that showed comparable 3 month results to radiofrequency ablation catheters with a mean office and home blood pressure reduction of $-36/-17$ mm Hg and $-22/-12$ mm Hg, respectively. Recent clinical trials using the PARADISE ultrasound ablation catheter include the RADIANCE-HTN and the REQUIRE trial.[57] The RADIANCE-HTN trial was designed to evaluate patients in 2 cohorts, RADIANCE-HTN SOLO (patients with mild-to-moderate hypertension, randomized while off antihypertensive medications), and RADIANCE-HTN TRIO (patients with uncontrolled resistant hypertension, despite receiving 3 antihypertensive medications). The REQUIRE trial was designed to evaluate patients with resistant hypertension on standard of care medication in Japan and Korea. Six-month results from the RADIANCE-HTN SOLO trial, a randomized, blinded, sham-controlled trial, showed sustained reduction in daytime ambulatory systolic BP to a greater extent than sham (-18.1 ± 12.2 vs -15.6 ± 13.2 mm Hg, $P = 0.024$), respectively, with no major adverse events in either group.[58] Follow-up is ongoing through 3 years to assess longer term safety and efficacy.

The RADIANCE-HTN TRIO and the REQUIRE studies are currently enrolling patients.

A pivotal study of the Recor medical paradise in stage II hypertension (RADIANCE II) was recently lunched with an objective to demonstrate the effectiveness and safety of the Paradise System in subjects with Stage 2 hypertension on 0-2 medications at the time of consent, and remained hypertensive after a 4-week washout period of drug discontinuation.[59] The study completion date is estimated at December 2020.

A recent 3-arm randomized trial (RADIOSOUND-HTN) performed head-to-head comparison of the different RSD devices and techniques, and randomly assigned resistant hypertension patients to a 1:1:1 block of (a) radiofrequency RSD of the main renal arteries; (b) radiofrequency RSD of the main renal arteries, side branches, and accessories; or (c) an endovascular ultrasound−based RSD of the main renal artery. There were significant blood pressure reductions in the ultrasound ablation group compared to the radiofrequency RSD group of the main renal artery (-13.2 ± 13.7 vs -6.5 ± 10.3 mm Hg) but no significant difference between the radiofrequency groups, and between the ultrasound ablation group and the side branch ablation group.[60]

The TIVUS-Therapeutic Intravascular Ultrasound Catheter System (Cardiosonic Ltd., Tel Aviv, Israel) has a miniaturized ultrasonic transducer located on the tip of a flexible catheter that emits high-intensity, nonfocused ultrasonic waves that penetrates the artery wall at a depth range of 0.5 mm to 10 mm, therefore allowing for more controllable, repeated and complete renal nerve ablation in the adventitia while sparing the endoluminal surface. This is done without the need for an occlusion cooling balloon. The phase I study of the TIVUS system demonstrated significant mean reductions in office blood pressure (systolic/diastolic) at 1, 3, and 6 months of $-26.1/-9.6$ mm Hg, $-28.0/-9.9$ mm Hg, and $-30.6/-14.1$ mm Hg ($P < 0.01$ for all), especially in individuals with combined systolic and diastolic hypertension, with no significant adverse events.[61]

The Kona Surround Sound system (Kona Medical Inc. Bellevue, Washington) is an externally delivered low-intensity, focused ultrasound energy to the renal nerves using Doppler based external ultrasound imaging guidance with real-time monitoring of the treatment area to track and correct for renal artery motion during treatment. The WAVE I trial was a first-in-man study evaluating the safety and efficacy of Kona Medical's Surround Sound RSD system in patients with office BP of at least 160 mm Hg and 24-h ambulatory BP of at least 135 mm Hg.[62] There were no device-related serious adverse events and there was a sustained decrease

in systolic blood pressure of approximately 27 mm Hg at 6-month follow up.

The WAVE II study demonstrated the safety and efficacy of successful renal nerve ablation using an optimized treatment protocol of 14 focused lesions produced over 2.8 minutes on each side compared to the 18 focused lesions over 12.6 minutes on each renal artery used in WAVE I trial.[62] However, the WAVE IV trial, which was a phase II randomized, sham-controlled, double-blinded trial of renal artery denervation in individuals with uncontrolled hypertension, was prematurely stopped because the data did not prove that antihypertensive efficacy of externally delivered focused ultrasound for RSD was greater than the sham effect.[63]

Pharmacological Ablation Technology

The pharmacological ablation technology uses a catheter-guided system that aim to locally inject therapeutic agents into the adventitial tissue, causing a maximal renal nerve ablation without injury to the vessel intima or media.

The Peregrine System Infusion Catheter (Ablative Solutions, Kalamazoo, MI), used for delivery of alcohol directly into the adventitial and periadventitial tissue of renal arteries was validated in a preclinical study of adult swine that demonstrated a linear dose response between the injected alcohol volume and norepinephrine reduction (up to 88% reduction with 0.6 mL of ethanol), and a significant circumferential renal nerve injury without detectable renal artery stenosis at 45 days.[64] The Peregrine System is being evaluated in the TARGET BP I and the TARGET BP OFF-MED randomized, sham-procedure controlled trials with an estimated primary completion date of December 2020 and September 2020, respectively.[65,66]

The Mercator Bullfrog Microinfusion Catheter (Mercator MedSystems Inc., San Leandro, California) is a catheter-guided system that was designed to locally and safely inject therapeutic agents through arterial walls into adventitial tissues. It is compatible with a 5-7 Fr introducer sheath and a 0.014" wires. The Bullfrog catheter is tipped with a balloon-sheathed microneedle which is inflated at low pressure (2 atm) to secure the system in the vessel for injection and sliding the microneedle through the vessel wall. A preclinical study of guanethidine monosulfate injection into renal artery periadventitial tissue resulted in time-dependent reduction in norepinephrine content and specific immune-mediated destruction of renal nerve at site of injection.[67]

Safety of Renal Sympathetic Denervation

The overall safety profile of RSD was shown in the preliminary 3-year safety result of the Symplicity Spyral cohort in the Global Symplicity registry. There were limited adverse events, and no instances of renal artery stenosis or reintervention.[68] 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%). The mean eGFR decreased from 80 ± 24 to 72 ± 26 ml/min/1.73m^2 between baseline and 3 years which was within the expected range.[69]

Physiologic and hemodynamic consequences of norepinephrine reduction on sympathetic response were evaluated in a substudy of the Symplicity HTN-2 trial in participants that underwent a cardiopulmonary exercise test. There was reduced blood pressure and heart rate during exercise, improved heart rate recovery, improved mean workload, and increased exercise time without compromising chronotropic competence[70,71] suggesting beneficial rather than detrimental effect of RSD on regulatory and counter-regulatory body hemodynamics.

There are concerns of renal artery reinnervation after RSD procedure which has been shown to occur in preclinical studies with regenerative nerve attempt as early as 7 days post-RSD,[72] however despite this morphological evidence of sympathetic regrowth, norepinephrine content has been shown to not fully recover to the predenervation level.[73,74] This may explain the sustained reduction in blood pressure observed following RSD. Long-term follow up of RSD patients are required to determine the functional significance of renal nerve regeneration after RSD.

Impact of Renal Denervation on Other Comorbidities

Congestive Heart Failure

The sympathetic nervous system has been implicated in the pathological remodeling of cardiac structures and its overactivation is a primary pathological component of the pathogenesis of heart failure. Renal norepinephrine spillover has been associated with combined end-point of all-cause mortality and heart transplantation in patients with heart failure.[75] The use of beta-blockers to downregulate pathological sympathetic signaling in heart failure significantly reduces cardiovascular morbidity and mortality.[76] It has therefore been postulated that removal of

sympathetic response in heart failure patients through RSD may attenuate progression of heart failure and reduce mortality. The REACH-Pilot study demonstrated improvements in both symptoms and exercise capacity in patients with chronic systolic heart failure 6 months after RSD.[77] Brandt et al[78] demonstrated that RSD decreased left ventricular mass index, and improved diastolic function, reduced interventricular septum thickness, decreased end-systolic volume, and improved ejection fraction.

Atrial Fibrillation

The ERADICATE-AF trial was designed to determine whether RSD when added to pulmonary vein isolation enhances long-term antiarrhythmic efficacy, and it demonstrated that among patients with paroxysmal atrial fibrillation and hypertension, RSD added to catheter ablation significantly increased the likelihood of freedom from atrial fibrillation at 12 months when compared with catheter ablation alone.[79]

Glucose Metabolism

Chronic compensatory sympathetic and neurohormonal activation are important contributors to the pathophysiology of many cardiovascular diseases including diabetes mellitus and metabolic syndrome. RSD was associated with reductions in fasting glucose, insulin and C-peptide levels, and mean 2-hour glucose levels during oral glucose tolerance test in patients with resistant hypertension.[80] However, the DREAMS-Study showed that RSD did not change median insulin sensitivity nor systemic sympathetic activity,[81] although this study lacked a proper control group and the sample size was small. Large randomized clinical studies are needed to further evaluate the impact of RSD on insulin resistance.

Obstructive Sleep Apnea

In a proof-of-concept Phase II trial,[82] RSD demonstrated sustained reduction in office and ambulatory blood pressure, and there was a significant decrease in obstructive sleep apnea severity (apnea/hypopnea index, 39.4 vs 31.2 events per hour). Witkowski et al[83] also demonstrated a decrease in apnea-hypopnea index at 6 months after renal denervation (median: 16.3 vs 4.5 events per hour).

Other Comorbidities

The attenuation of sympathetic outflow and the renin-angiotensin-aldosterone signaling by RSD has demonstrated improvement in pulmonary vascular remodeling and pulmonary hypertension;[84] gestational hypertension;[85] anxiety, depression, and self-assessed physical and mental status.[86]

Cost-Benefit Analysis

In a retrospective study to assess cost-effectiveness and long-term clinical benefits of RSD in resistant hypertensive patients in the Symplicity HTN-2 trial, a state-transition (Markov) model was used to predict the effect of RSD and standard of care on 10-year and lifetime probabilities of stroke, myocardial infarction, all coronary heart disease, heart failure, end-stage renal disease, and median survival. Median survival was 18.4 years for RSD compared to 17.1 years for standard of care. The incremental cost-effectiveness ratio was cost-saving to $31,460 per quality-adjusted life-year.[87]

Conclusion

The results from newly designed clinical trials conducted with the use of newly designed RSD catheters are encouraging and lend support to the concept that RSD is effective in reducing office and ambulatory blood pressures and may as well be as effective treatment in other clinical conditions associated with chronically elevated sympathetic activity.

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