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Proceedings from the Society of Interventional Radiology Foundation Research Consensus Panel on Renal Sympathetic Denervation

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ABBREVIATIONS

BP = blood pressure, CHF = congestive heart failure, HTN = hypertension, MSNA = muscle sympathetic nerve activity, NE = norepinephrine, LV = left ventricular, OSA = obstructive sleep apnea, PET = positron emission tomography, PAREPET = prediction of arrhythmic events with positron emission tomography, RCP = research consensus panel, RDN = renal denervation, RSNA = renal sympathetic nerve activity

In 1948, Smithwick and others (1,2) reported on operative thoracolumbar sympathectomy to treat hypertension (HTN). In a study of patients with uncontrolled HTN who underwent thoracolumbar sympathectomy, 45% of 1,266 patients maintained significant improvement in blood pressure (BP) 5 years later (3). However, this procedure was also associated with significant morbidity and orthostatic hypotension and was abandoned in the 1960s with the widespread advancements in, and availability of, effective pharmacologic therapy. In the 1970s, operative ligation of the sympathetic fibers in the perirenal space was considered a contributor to the benefits of renal artery surgery for treatment of renovascular HTN or chronic kidney disease (4). More recently, convincing evidence has emerged that chronic elevation of sympathetic nervous system activity is a major contributor to the complex pathophysiology of essential HTN and in particular resistant HTN (5,6).

In 2007, an endovascular radiofrequency (RF) ablation catheter that could safely reduce renal sympathetic innervation was first demonstrated (7). Transcatheter endovascular renal denervation (RDN) using RF ablation was used clinically shortly thereafter and has since demonstrated dramatic short-term and midterm benefits for the treatment of resistant HTN (8–10).

The breadth and number of clinical trials in this field have expanded rapidly. Additional findings from mostly small, uncontrolled, observational studies have suggested numerous favorable cardiovascular responses to RDN that are in need of corroboration (11–16). The potential for early clinical adoption has also driven the development and clinical testing of multiple new devices for ablation of the perirenal sympathetic nerve fibers (17,18).

Many questions remain about RDN, including mechanisms of action of RDN, local renal versus systemic effects of denervation, local long-term effects on the vascular endothelium and wall, methods for selecting appropriate candidates for RDN, evaluation of potential alternative clinical indications, comparisons of study populations and devices, extent of RDN, and development of better outcome measures after RDN (6,19,20). The goal of this article is to report on the proceedings of a Society of Interventional Radiology (SIR) Foundation Research Consensus Panel (RCP) on RDN. A secondary

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goal is to develop a consensus on the clinical research opportunities specific to RDN, while evaluating the potential for broader applications of perivascular denervation for the treatment of other diseases.

METHODS

Panel Membership

On October 21, 2013, the SIR Foundation assembled a RCP meeting for the development of a research agenda on RDN. Participating in the meeting were 11 expert panelists, including 2 cardiologists, 6 interventional radiologists, 1 nephrologist, and 2 physiologists; the U. S. Food and Drug Administration and the Agency for Healthcare Research and Quality; and industry representatives from major companies involved in the production of endovascular devices for treatment of RDN.

Agenda Methodology

Before the RCP meeting, the expert panelists received an agenda to facilitate the goals of (*a*) establishing a common foundation of working knowledge for dialog among the panelists; (*b*) identifying gaps in current knowledge; and (*c*) providing recommendations for basic science, preclinical, or multicenter clinical research opportunities. Before the meeting, 12 topics for discussion were determined through consensus of the panelists. Selected topics were presented to the entire panel by the RCP panelists with expertise in that area.

Each panelist was asked to give a focused (10 minutes) presentation about his or her assigned topic. Specifically, panelists were asked to (*i*) define the most important clinical questions that could realistically be answered through pivotal multiinstitutional clinical trials or registries, (*ii*) describe the most promising future directions that merit preclinical or early clinical exploration, and (*iii*) outline how SIR investigators can best engage in these initiatives.

Afterward, a round-robin discussion was held to examine important research questions, to explore potential opportunities for future research studies or substudies within the currently available research initiatives, and to consolidate similar ideas into a short list of potential research topics. Thereafter, invited comments from government and industry representatives were heard. Finally, a consensus was reached on a single research initiative for multispecialty collaborative development.

RESULTS

The panel produced 12 presentations, which are summarized in this article and form the foundation for the conclusions from the RCP. Included in this summary are the most significant unanswered questions about RDN that the panelists thought still needed to be addressed.

Role of Afferent and Efferent Renal Sympathetic Nerves in HTN

The cell bodies of preganglionic sympathetic neurons that innervate the kidneys are located in the lower thoracic and upper lumbar spinal cord and send axons out of the central nervous system to make synapses with postganglionic neurons in peripheral ganglia. Sympathetic nerve fibers from these postganglionic neurons terminate at the renal vasculature, tubules, and juxtaglomerular cells, of which the last-mentioned are the source of renin. The kidneys also have afferent nerves that carry information from mechanoreceptors (responding to increases in renal pelvic pressure) and chemoreceptors (responding to changes in chemical composition of the urine) to the central nervous system. These sensory receptors are especially prominent in the renal pelvic wall (6). Nerves to and from the kidneys are derived from the celiac plexus, lumbar sympathetic nerves, and superior mesenteric ganglion.

There is considerable evidence that increased sympathetic activity, more specifically, increased renal sympathetic nerve activity (RSNA), plays an important role in the pathogenesis of HTN (6). Because of technical limitations preventing direct recording of nerve activity from internal organs, organ-specific sympathetic activity has been determined using biochemical techniques. Although technically challenging, RSNA can be quantified by measuring the spillover of norepinephrine (NE) into the renal venous circulation. Renal NE spillover = $[(C_V - C_A) + C_A(NE_E)] \times RPF$, where C_V is the plasma NE concentration in the renal vein, C_A is the arterial plasma NE concentration, NE_E is the fractional extraction of radiolabeled NE (infused at a constant rate) in transit of blood through the kidneys, and RPF is renal plasma flow. Studies employing renal NE spillover measurement have demonstrated that renal NE spillover is increased in primary HTN (6). In the initial proof-of-principal cohort of subjects with resistant HTN, NE spillover was reduced by an average of 47% when measured 15–30 days after RDN with the Symplicity (Medtronic, Santa Rosa, California) system (21). This decrease in NE spillover was associated with a reduction in office BP measurements over 6 months of 22/12 mm Hg. It is possible that more extensive denervation could result in a greater and more consistent reduction in BP.

Selective afferent RDN by thoracolumbar dorsal rhizotomy (T9–L1) in rats has been reported to attenuate HTN in rats (22). The antihypertensive effects are believed to abolish sensory information from renal mechanoreceptors and chemoreceptors to central integrative centers involved in the regulation of sympathetic activity to the peripheral circulation. Patients with chronic renal disease who are receiving maintenance hemodialysis treatment have HTN and increased muscle sympathetic nerve activity (MSNA), which diminishes after removal of the diseased kidneys; this also supports the concept that

renal afferents contribute to HTN by increasing global sympathetic activity (23,24).

The first reported patient to undergo RDN demonstrated a substantial reduction in whole-body NE spillover and MSNA measurements at 1 and 12 months (8). This report along with speculations made in the initial proof-of-concept study (21) led to the idea that *afferent* signals from the kidneys to the central nervous system lead to increased *efferent* sympathetic nerve activity throughout the circulation in patients with resistant HTN and that renal nerve ablation decreases arterial pressure not only by diminishing *efferent* RSNA but also by attenuating global sympathetic activity as a result of disrupting renal *afferent* nerve signaling.

The first Symplicity trial demonstrated long-term reductions in MSNA after RDN in a larger patient population (N = 24) (25). However, in this study, the reductions in MSNA (approximately 10%) measured 3 months after RDN were considerably less than what had been reported in the earlier report. More recent clinical studies conducted by other investigators using the Symplicity Catheter System have failed to observe long-term reductions in MSNA consistently after RDN (26,27). The issue of whether RDN truly leads to a decline in global sympathetic activity in patients with resistant HTN as a result of diminishing renal afferent nerve activity is unresolved.

It is also unclear if catheter-based renal nerve ablation always leads to sufficient disruption of renal nerves to cause lowering of BP. There is some clinical evidence that unilateral ablation is insufficient (28). Because catheter ablation denervates efferent and afferent nerves, it is difficult to ascribe the resulting cardiovascular effects to the destruction of a particular class of nerves. Future studies may benefit from a clinically applicable measure to confirm and quantify the degree of denervation needed to achieve favorable cardiovascular responses.

Another area of interest for investigation is the confounding issue of sustained long-term reduction in BP despite the known phenomenon of nerve regeneration. Nerve regeneration occurs in animal models and is likely to occur in humans (29,30).

Definition of Resistant HTN and Its Potential Impact on Clinical Results

The published data concerning the antihypertensive effects of RDN have been solely based on the treatment of patients with resistant HTN. Resistant HTN has been defined by the American Heart Association as a persistent elevation of BP despite the concurrent use of three or more antihypertensive agents at optimized dosing, with one of the medications being a diuretic (31). Even with advancements in medical therapy, resistant HTN likely affects 3.4%–30.9% of hypertensive patients (32), yet RDN trials consider only 0.8% of hypertensive patients to be eligible for RDN (32).

Only a small percentage of patients with apparent resistant HTN are truly refractory to drug therapy owing to the inclusion of patients with white coat HTN, patients who are noncompliant with their medical regimen, and patients treated with suboptimal combinations and doses of drugs. Many of the trials performed outside of the United States have used office BP measurements to enroll patients and monitor outcomes after RDN. Trials currently underway or in progress in the United States use 24-hour ambulatory BP monitoring, in addition to office-based measurement, to reflect more accurately real-world clinical outcomes achieved with RDN. These newer trials being performed in the United States may find very different results from these prior trials (33,34).

Current Clinical Trials

Published data from clinical trials of RDN as a treatment for resistant HTN (21,35,36) have shown significant and sustained office-based BP reductions at 36 months of follow-up. Subgroup analysis and phase II testing have also shown improvements in other diseases associated with autonomic dysfunction, such as sleep apnea, insulin-resistant diabetes, left ventricular (LV) hypertrophy, tachyarrhythmias, and congestive heart failure (CHF) (13,16). Ongoing RDN clinical trials for the treatment of resistant HTN continue this trend of investigating other potential benefits associated with RDN.

To date, the Medtronic Symplicity catheter has been the best-studied device on the market, having obtained European Certification (CE Mark). The first U.S. trial approved by the Food and Drug Administration (Symplicity HTN-3), the most rigorous trial to date with sham surgery and double blinding, has completed 6-month follow-up. Unpublished results suggest that there is not clinical efficacy. This is likely to have a significant impact on the design and implementation of additional studies. There are currently 90 RDN trials using various devices registered on www.clinicaltrials.gov. Only 8 of the 90 RDN trials intend to include centers or subjects in the United States, with most of the trials enrolling patients from Europe and Australia and a sizable minority involving centers in China and Russia. Of these studies, 32 plan to research the Symplicity catheter (Medtronic Ardian, Inc, Mountain View, California); 12 plan to look at the Celsius ThermoCool catheter (Biosense Webster, Diamond Bar, California); 8 plan to look the EnligHTN multielectrode catheter (St. Jude Medical, St. Paul, Minnesota); and the remainder plan to look at the Paradise catheter (ReCor Medical, Inc, Palo Alto, California), the Kona Surround Sound system (Kona Medical, Inc, Bellevue, Washington), the Vessix V2 catheter (Vessix Vascular, Inc, Boston Scientific, Laguna Hills, California), or the TIVUS (Therapeutic IntraVascular UltraSound) catheter system (CardioSonic, Ltd, Tel Aviv, Israel).

Most of the upcoming trials plan to study patients with resistant HTN. Many of these trials plan to look at subpopulations of patients with resistant HTN, such as patients with comorbid obstructive sleep apnea (OSA), metabolic syndrome, insulin-resistant diabetes, chronic kidney disease, atrial or ventricular tachyarrhythmias, heart failure, autosomal dominant polycystic kidney disease, acute coronary syndrome, and stroke. This breadth of subpopulations for evaluation reflects a heavy emphasis on exploring new cardiovascular applications of this technology. RDN is expected to be the standalone experimental intervention in most of these trials with a few investigating the concomitant use of cardiac electrophysiology interventions or coronary artery interventions.

Most of the proposed trials are designed as randomized controlled trials, some of which are expected to have sham control arms. Projected patient enrollments range from 8–5,000, with most trials intending to enroll < 200 subjects. Projected completion dates of these trials are mostly before 2018.

Changes in BP is to be the primary outcome measure in most of these trials. Proposed methods of BP measurement include home, office, and ambulatory readings. The most rigorous method of measuring BP in these trials is 24-hour ambulatory BP monitoring. Ambulatory BP monitoring is likely to be the metric of choice in future trials. Other projected outcome measures include changes in baseline autonomic nervous system function, as reflected by changes in MSNA and levels of circulating catecholamine; changes in insulin resistance, as reflected by fasting glucose and hemoglobin A_{1c} levels; renal function based on albuminuria, serum creatinine values, and estimated glomerular filtration rates; activation of the renin-angiotensin-aldosterone system; control of tachyarrhythmias, looking at recurrence rates measured by implantable cardioversion device output or symptomatic recurrence with hospitalization; cardiac geometry and hemodynamics; quality of life; changes in medication use; and cost-effectiveness (37–43).

There are opportunities for future investigation with real-time monitoring of the progress and success of RDN perhaps by establishing a standard for measuring levels of renal and global sympathetic activity before, during, and after ablation in an effort to predict clinical outcomes better. Investigating whether trial participants altered their diet, exercise pattern, other cardiovascular risk factors, or medication compliance might also help to define specific variables that secondarily affect the long-term trends in BP response after RDN therapy. Evaluating a cohort of patients with and without an associated anxiety disorder might also help in further understanding which patients are best served by RDN therapy.

Role of RDN in Renal Insufficiency

There is increasing interest in determining what effect ablation devices and RDN therapy have on renal function, particularly when treating patients with resistant HTN and chronic kidney disease. It is possible that RDN may increase the glomerular filtration rate, but it is unclear if this effect is beneficial or damaging to remnant nephrons in the long-term. Case reports suggest that renal function can potentially improve in the short-term after denervation (44). However, long-term data to support this conclusion are scarce. Because the safety of this technology in subjects with stage 4 or 5 renal dysfunction has not been determined, it is unclear how this mechanism could account for the putative link between activation of renal afferents, as seen in acute renal injury experimental models (18,19,37), and stimulation of central sympathetic outflow because RDN has been restricted to patients with resistant HTN in the absence of overt renal disease. Patients with kidney disease provide an opportunity for advancement in RDN research. Including patients with chronic kidney disease in controlled trials would give us more insight into the effect of sympathetic hyperactivity and the utility of RDN in affecting the progression of renal dysfunction in this patient population.

RDN in the Presence of Renal Artery Stenosis

The presence of a hemodynamically significant renal artery stenosis excludes potential patients from the current RDN clinical trials. RDN in the presence of fibromuscular dysplasia or after successful renal artery stent placement for atherosclerotic stenosis has been reported (45,46). The question of the safety and the therapeutic effect of RDN in the setting of renal artery stenosis and whether or not the combination of angioplasty or renal artery stent placement with RDN could have an additive effect in the management of renin and sympathetically mediated HTN is raised.

There is a role for renal artery imaging after the procedure to identify if a hemodynamically significant stenosis has developed after RDN therapy. Screening before the procedure may be very important in determining candidacy for RDN (eg, occult stenosis, artery size and branching pattern). All the current clinical trials have included a diagnostic angiogram for evaluation of renal artery anatomy before any RDN therapy. This protocol is unlikely to change as long as the experimental treatment is delivered via a transarterial, catheter-based platform. Ultrasound (US), computed tomography (CT) angiography, and magnetic resonance (MR) angiography all may be useful for screening and planning before RDN, but the relative benefit of these noninvasive imaging modalities needs to be evaluated further and validated (47,48).

Application of RDN in OSA

OSA is characterized by recurrent episodes of respiratory airflow cessation caused by upper airway

inspiratory obstruction resulting in decreased oxygen saturation. OSA is estimated to affect 24% of middle-aged men and 9% of middle-aged women. OSA is often found to coexist in other diseases associated with dysautonomia, such as HTN, impaired insulin tolerance, and obesity (43). Several reports have shown that the prevalence of HTN is greater in patients with OSA and vice versa and that OSA increases the risk of cardiovascular events and impairs the control of BP in hypertensive patients. OSA and HTN are also believed to be causally related, possibly through sustained activation of the sympathetic nervous system (49). However, the precise mechanism whereby OSA leads to persistent sympathetic activation and the effect of RDN on OSA are unclear.

Witkowski et al (16) showed that OSA was a consequence as well as a cause of increased sympathetic activity in patients who underwent RDN for resistant HTN. These investigators also reported that the apnea-hypopnea index improved in 8 of 10 patients 6 months after RDN. A possible mechanistic link between the improvement in OSA indices and RDN was provided by an earlier study showing that displacement of fluid from the legs to the neck overnight strongly relates to the severity of OSA in patients with both controlled and resistant HTN (50). By reducing rostral fluid shifts as a result of increasing renal excretory function and reducing body fluid volume, RDN may decrease the severity of OSA by diminishing peripharyngeal fluid accumulation that might otherwise predispose to upper airway obstruction. Additionally, the sympathetic nervous system is thought to control venous compliance. Denervation can also increase venous compliance, leading to increased capacity, which may alleviate the blood pooling in the peripharyngeal tissues. Better BP control can also contribute to apnea improvement through its influence on baroreflex reactivity and central respiratory control (13,16). RDN in patients with resistant HTN and OSA might attenuate the effects of activation of the sympathetic nerves.

The possibility that the decrease in BP may independently contribute to the attenuation of OSA also must be considered. Additionally, it needs to be established if the response of the sympathetic nervous system to RDN in OSA can be quantified. Randomized controlled clinical trials with sympathetic activity measurements are needed to ascertain if and when RDN is a potential treatment option for patients with OSA.

RDN in Insulin Resistance

Many subjects with resistant HTN are obese and have insulin resistance. In 37 patients with resistant HTN, Mahfoud et al (13) reported substantial reductions in fasting glucose, insulin levels, and BP 1 and 3 months after renal nerve ablation. In addition, RDN reduced elevated 2-hour glucose levels during a glucose tolerance test. This study suggests that RDN reduced two leading cardiovascular risk factors in hypertensive patients: BP and diabetic status.

A case report of two patients suggests that patients with polycystic ovarian syndrome, which is often associated with HTN, obesity, OSA, and insulin resistance, may demonstrate better BP and glucose tolerance after RDN (11). Although these studies provide no mechanistic insight into the beneficial effects of RDN on glucose metabolism, the authors speculate that the improved insulin resistance was secondary to suppression of general sympathetic activity. The rationale for this speculation was based on observations that sympathetic activation acutely causes peripheral vasoconstriction, reduced skeletal muscle blood flow, and reduced glucose uptake. However, the relevance of these transient effects on the chronic hyperinsulinemia and hyperglycemia as well as HTN associated with obesity is unclear. In this regard, despite increases in sympathetic outflow to several vascular beds, including the skeletal musculature, there is little evidence that basal blood flow is decreased in these tissues in obesity. As a first step, additional studies are needed to confirm these observations in obese patients with resistant HTN and insulin resistance who are treated with RDN. Future studies should answer how RDN diminishes insulin resistance and what is the best way to measure this insulin resistance effect.

Monitoring RSNA during RDN

The ability for real-time monitoring of the success of RDN has been repeatedly emphasized in the literature. Confirmation of sympathetic denervation in preclinical studies traditionally has been measured by changes in tissue catecholamine levels and NE spillover before and after RDN (51). No clinical test is currently available to confirm the effect of RDN at the time of the treatment. Also, no reliable method is available to assess the extent of sympathetic nerve injury or ablation during the procedure. Availability of measures of sympathetic activity would allow the real-time monitoring of RDN therapy and its correlation to the degree of clinical response. This information would help determine how much denervation is necessary and which device and method can best achieve it.

Noninvasive Imaging during RDN

Four potentially relevant areas of clinical imaging research with RDN include functional brain MR imaging, imaging of sympathetic activity in the kidney, renovascular imaging, and renal perfusion imaging.

Functional MR Imaging of the Brain. The strong connection between central sympathetic activity and BP suggests that brain imaging may be an important area for RDN research. Functional MR imaging of central

sympathetic activity after RDN is relatively unexplored. In one study, functional MR imaging scans were correlated with MSNA using peroneal nerve electrode measurements in human volunteers (52). MSNA and functional MR imaging scans covaried best in the left midinsula, bilateral prefrontal cortex, posterior cingulate cortex, and precuneus. Additional experiments assessing human functional MR imaging activity with baroreflex (simulated using deep inspiration) identified an association between BP, baroreflex receptor activity, MSNA, and certain regions of the brain (53). If functional MR imaging findings correlated with renal sympathetic overactivity, imaging could potentially be useful in predicting the clinical response if central neural activity is remodeled after RDN.

Imaging of RSNA. Although the peripheral sympathetic nervous system is beyond spatial resolution of CT and MR imaging, tissue characterization of inhomogeneity of sympathetic nerve receptors in cardiac muscle using a positron emission tomography (PET) compound has been accomplished. The PAREPET (prediction of arrhythmic events with positron emission tomography) study tested the hypothesis that a paucity of cardiac muscle sympathetic uptake, measured using carbon 11–meta-hydroxyephedrine, was associated with sudden cardiac events in patients with underlying ischemic cardiomyopathy (54). The use of this or similar PET agents to label neurotransmitters in the periphery, kidney, or other sites is a potential area of research into the effect of RDN on the kidney.

Although anatomic imaging of the perirenal sympathetic nerves has not yet been reported, advances that might make this goal possible include optical coherence tomography, vascular US, and molecular imaging. Even quantification of perivascular temperature after denervation could help characterize successful outcomes after treatment or predict nonresponders.

Renal Perfusion Measurement. Reducing renovascular resistance through RDN should improve renal perfusion. Renal perfusion is important to kidney function and BP control. However, a clinical trial of 19 patients who underwent RDN and noncontrast perfusion MR imaging failed to demonstrate a significant change in renal perfusion 1 day or 3 months after RDN (55), but renovascular resistance was demonstrated to be significantly reduced. These preliminary findings raise the question of whether or not a large-scale study of perfusion MR imaging would demonstrate a change in renal perfusion after RDN, and, if yes, would low perfusion on MR imaging performed before a procedure be an indication for RDN? Conversely, if there is a change in renovascular resistance but not in renal perfusion with RDN, would the effect of RDN in renal insufficiency be less likely to be beneficial on renal function? In patients with chronic HTN, are there any changes within the kidney vasculature that may take longer to normalize, and, if so, do these techniques to estimate changes in renovascular resistance or perfusion need to be measured at several time points over many months?

Renal Diffusion Imaging. Another potentially useful tool in analyzing the effect of RDN on the kidney is diffusion-weighted MR imaging (56,57). This technology measures water diffusion in cortical or medullary tissue, and this diffusion may be an early marker of renal disease. Differences in split kidney function may be helpful in identifying RDN candidates or measuring asymmetric responses to RDN (56–58). However, preliminary studies indicate that this technique is not useful for identifying early microvascular changes of HTN (56).

Tachyarrhythmias and Sympathetic Hyperactivity

The autonomic nervous system modulates cardiac electrophysiology and has a profound effect on cardiac automaticity (59). The impact of RDN in patients with refractory atrial fibrillation and resistant HTN was assessed in a study in which 27 patients were randomly assigned to pulmonary vein isolation alone or pulmonary vein isolation plus RDN (60). Besides significant reductions in BP, patients in the pulmonary vein isolation plus RDN group experienced fewer episodes of atrial fibrillation at follow-up. It was speculated that the effect of RDN may have been due to reduction in cardiac sympathetic stimulation and a reduction in BP of the patients. However, can RDN influence cardiac arrhythmias independent of reductions in BP? A preclinical study in a dog model of obesity-induced HTN demonstrated that HTN was associated with tachycardia, attenuated chronotropic baroreflex responses, and reduced heart rate variability (a risk factor for life-threatening arrhythmias) (60). Both chronic baroreflex activation and RDN abolished HTN. However, only chronic baroreflex activation attenuated the tachycardia and restored cardiac baroreflex sensitivity and heart rate variability. This study suggested that baroreflex activation therapy (but not RDN) in patients with resistant HTN, who are commonly obese, may diminish the risk of cardiac arrhythmias by lowering BP and improve cardiac baroreflex sensitivity by shifting autonomic balance toward reduced sympathetic drive and increased vagal activity. Areas for potential research in this field would include identification of the effect of RDN on the synchronization of cardiac activity and how to separate the beneficial effects of BP changes caused by RDN from its electrophysiologic effect on arrhythmias.

RDN for Prevention and Management of CHF

Increasing evidence demonstrates overactivation of the sympathetic nervous system in patients with CHF (51,61–63). Evidence also suggests roles for both renal efferent and afferent nerve activity in the development and maintenance of CHF. The physiology of patients with CHF suggests that (*i*) RDN of efferent sympathetic nerves would reduce inappropriate renin release and sodium retention and improve renal blood flow, and (*ii*) RDN of afferent sensory nerves would attenuate the contribution of the kidney to centrally mediated sympathetic nervous system overactivity (63).

Chronic CHF can be categorized broadly into two subtypes: left ventricular (LV) systolic dysfunction with impaired ejection fraction and LV diastolic dysfunction and preserved ejection fraction. LV systolic dysfunction is associated with neurohormonal hyperactivity as a compensatory mechanism to maintain cardiac output in the face of declining cardiac function. Sympathetic nervous system hyperactivity is present in these patients as evidenced by increased plasma catecholamine levels, elevated central sympathetic outflow, and heightened NE spillover from activated cardiac sympathetic nerve terminals (63). There is also an increase in NE spillover from the kidney, supporting a role for increased renal efferent activity in sodium and water retention in humans with chronic CHF. Intrarenal adrenergic (sympathetic) blockade has been shown to result in natriuresis. Treatment with a centrally acting α_2-adrenergic receptor agonist, clonidine, at modest doses significantly attenuates cardiac activity and RSNA in patients with chronic CHF associated with systolic dysfunction.

However, data supporting the presence of chronic sympathetic nervous system hyperactivity in patients with heart failure and normal LV ejection fraction (ie, diastolic heart failure) are limited. Support for the use of RDN in patients with normal LV ejection fraction heart failure and HTN comes from a report indicating regression of LV hypertrophy after RDN independent of its effect on lowering BP (64). RDN in patients with heart failure and normal LV ejection fraction is presently being examined as part of the multicenter randomized controlled DIASTOLE (DenervatIon of the renAl Sympathetic nerves in hearT failure with nOrmal Lv Ejection fraction) Trial (65). The primary objective of this trial is to investigate the effect of RDN on cardiac geometry by means of Doppler echocardiographic parameters. Secondary objectives include safety of RDN and a comparison of changes in LV mass, LV volume, LV ejection fraction, and left atrial volume as determined by MR imaging. Neurohumoral activity, BP, heart rate variability, exercise capacity, and quality of life also is to be assessed. The results of this trial will provide important information regarding the potential role of RDN in the treatment of patients with CHF and normal LV ejection fraction. A weakness in the protocol of the DIASTOLE trial is that there are no specific recommendations about what heart failure or antihypertensive medications the patients should be taking.

Future study should also compare RDN with other strategies to decrease sympathetic nervous system activity, such as device-dependent chronic baroreceptor stimulation or carotid body removal or ablation, and require hard endpoints such as decreased hospitalizations and decreased mortality compared with patients treated with established therapies. If RDN is beneficial in patients with CHF, determining patient selection criteria would be important to incorporate RDN as a cost-effective therapeutic strategy. Biomarkers and treatment algorithms are needed to identify patients with sympathetic nervous system hyperactivity who are likely to benefit from RDN.

Other Minimally Invasive HTN Therapies

Use of US energy as a potential method to ablate renal nerves is an attractive option because US is readily available and can be performed in a focused or nonfocused manner, with limited or no radiation, and using a transcatheter or an extracorporeal approach. Several model designs are being tested; however, no currently active clinical trials in the United States are employing these devices.

The TIVUS catheter system for RDN is a high-intensity, nonfocused ultrasonic, 0.014-inch-based catheter system that employs a 6-F guide sheath to facilitate placement of the catheter. It is anticipated that the treatment time will be $<$ 10 minutes with this device. No data from human use are available, but preclinical data from 80 pigs have been used to determine optimal treatment parameters. Tissue TE concentrations at 30 and 90 days after treatment in animal studies have shown a $>$ 50% decline, consistent with successful renal nerve ablation, and coagulative necrosis of the nerves was also seen at histologic analysis. In addition, no intimal injuries in the renal arteries were evident either by angiography or histologic evaluation at 30 and 90 days. Potential advantages of this system include short procedure times, real-time assessment of the spatial location of the applied energy, easier treatment of renal arteries with early bifurcations, and minimum energy deposition on the luminal surface of the artery.

The Paradise system is a balloon-catheter system in which a low-pressure balloon centers the cylindrical US source and allows for cooling of the arterial wall via a circulating coolant within the balloon, while high-frequency nonfocused US energy is emitted circumferentially. The sound waves pass through the surrounding fluids and generate frictional heating of soft tissues at a depth where the sympathetic nerves in the adventitia of

the renal arteries are damaged circumferentially with a single emission. Preclinical data in 43 pigs showed consistent energy delivery, histologic evidence of renal nerve ablation, a 72% reduction in tissue NE levels after treatment, and minimal endothelial damage. The first-in-man study, which was conducted in South Africa on 15 patients, demonstrated a beneficial effect, with a persistent decrease in office systolic and diastolic BPs of 32 mm Hg and 17 mm Hg in the 11 patients available for follow-up at 6 months. The average heating time was 4.3 minutes per patient, and all treatments were done with conscious sedation and analgesia only (66). The REALISE (REnAL denervation by ultraSound transcatheter Emission) study is also currently enrolling at two sites in France (goal, N = 20). The device received CE Mark approval in December 2011, and the ACHIEVE (trAnsCatHeter Intravascular ultrasound Energy deliVery for rEnal denervation) study is currently enrolling at nine European sites (goal, N = 50) as a post–market approval study. Potential advantages of the Paradise catheter system include (*a*) a low-pressure balloon that centers the device and circulates cooling fluid, (*b*) uniform and circumferential treatment of the perirenal sympathetic nerves with a single sonication, and (*c*) a short treatment time.

In an attempt to eliminate the need for an intravascular approach for RDN, the Kona Surround Sound system delivers low-intensity focused US using an extracorporeal approach and US guidance. Low-intensity focused US is targeted at the tissue around the renal arteries and results in ablation of the renal sympathetic nerves by mechanical vibration and generation of thermal injury. Preclinical data from a pig model showed > 50% reduction in tissue NE levels and histologic evidence for nerve ablation. In addition, first-in-man data (N = 24) from the Well-Being of Adolescents in Vulnerable Environments (Wave) I study showed a reduction in office-based systolic and diastolic BPs of 29 mm Hg and 12 mm Hg at 24 weeks (67). The Wave II study (N = 18) has been completed, and results are pending analysis. The Wave III study involves Doppler-based targeting and tracking and is currently enrolling outside the United States. The Wave IV study is to be a randomized controlled study (China, Europe, and United States) with a target start date of January 2014. A cost comparison estimation based on the Wave I study with transcatheter-based denervation suggests a potential total cost savings benefit of > 50% (approximately $15,000 vs approximately $5,000) with the use of extracorporeal low-intensity, focused US. In addition, cadaveric studies have revealed that the distance from the parent artery to the renal sympathetic nerves can be > 10 mm. This distance is not uniform, with > 80% of the nerves being > 1.5 mm from the intimal surface and an average nerve distance from the endothelium being 3.2 mm (Virmani R, personal communication, October 2013).

There may be some benefit for an extracorporeal approach to ablation of the renal sympathetic nerves. Other potential benefits to using an externally applied focused US source include (*a*) no need for an arterial puncture or use of radiation, (*b*) real-time US guidance and thermometry, (*c*) an ability to target multiple renal arteries and variant anatomy, (*d*) use of three-dimensional modeling treatment planning to optimize denervation, (*e*) ability to treat the full complement and full thickness of the periadventitial sympathetic nerves, and (*f*) less likelihood of damaging the renal artery endothelium and intima.

Preliminary data from preclinical studies in China using the extracorporeal Chongqing Haifu Medical Technology system (Chongqing, China) employing high-intensity focused US with color flow Doppler imaging guidance in 18 dogs showed a significant decrease in tissue NE levels and systolic and diastolic BPs at 28 days. The mean procedure time was 27.4 minutes (68).

The use of a transarterial or extracorporeal method for delivery of US energy for renal sympathetic nerve ablation appears to be feasible with demonstrable renal nerve ablation. In addition, US technology may allow for real-time verification of treatment location, while monitoring in vivo tissue temperature, with minimal thermal energy delivery to the endothelium and intima.

The other more recent innovation is percutaneous injection of sclerosants to ablate the perirenal sympathetic nerves. The sympathetic nervous system is tightly bundled within the perirenal space and is accessible under percutaneous needle guidance using MR imaging, CT, or US (69,70). Preliminary studies of RDN using image-guided, percutaneous instillation of sclerosants suggest similar results to endovascular ablation techniques (70).

Beyond RDN, there are other denervation technologies and techniques to consider. One in particular is the implanted carotid baroreflex stimulator. Electrical activation of the carotid baroreflex has been shown to decrease BP, heart rate, and sympathetic activity and to increase renal excretory function in the long-term in both preclinical studies and clinical trials in patients with resistant HTN (71–73). Because of deficiencies in trial design, the Rheos pivotal randomized trial (CVRx, Minneapolis, Minnesota) of 265 patients did not demonstrate the primary endpoint of acute and sustained BP control in patients with resistant HTN (74). The ancillary endpoint of sustained systolic BP < 140 mm Hg did demonstrate that 42% in the treatment group versus 24% in the control group achieved the target BP at 6 months ($P = .005$). Since the Rheos study, the device has been further miniaturized (Barostim neo). Further investigation of sympathetic denervation compared with carotid body parasympathetic stimulation for BP control and cardiac complications of HTN or sympathetic overstimulation is indicated.

How future clinical studies will validate the efficacy of RDN devices, comparing the various techniques of RDN and the effects of techniques and devices on patient outcomes, will become very important as technology in this arena evolves. Predicting which patients will be nonresponders, better defining what anatomic location to treat (eg, proximal, distal, accessory arteries), treatment guidance and monitoring, developing more precise targeting, and minimizing nontarget injury are foci of further evaluation.

Denervation in Other Territories

There are other potential clinical applications for perivascular autonomic denervation (75). The role of the sympathetic and parasympathetic nervous systems in many disease states and in the control of the various body functions is well recognized. The encouraging results of RDN suggest attention should also be focused on modulation of other metabolically active organs, such as the liver and pancreas, through transvascular, extracorporeal, or percutaneous denervation of sympathetic fibers along the hepatic artery or portal vein. The role of these nerves in the control of glucose and lipid metabolism in the liver is being increasingly recognized (76,77). Hepatic artery and portal vein denervation may be a logical next territory for investigation for diabetes mellitus and metabolic syndromes (78,79). Preclinical studies suggest that portal vein denervation is associated with increased serum levels of triglycerides and cholesterol but reduced serum glucose. Whether these results would be seen with hepatic artery denervation is currently under investigation. Early surgical reports indicate hepatic periarterial sympathectomy can relieve jaundice resulting from hepatitis (79). Other observations in human subjects after liver transplantation also support the role of afferent nerves in sympathetic activity (80). These observations suggest that hepatic denervation may have a protective role in certain conditions, while being potentially deleterious in others. Further studies are necessary to delineate better the role of perivascular nerves in the function of liver and pancreas as well as their systemic effects.

As with RDN, there are numerous unanswered questions in hepatic artery and portal vein denervation that offer important areas for both preclinical and clinical investigation. First is to delineate the full effects of denervation on various metabolic pathways controlled by the liver and pancreas. Beyond that, the optimal location of denervation or stimulation (proximal such as celiac axis or more distal such as proper hepatic artery), the best method of nerve destruction or stimulation (energy-based vs chemical), the degree of denervation required, and the development of preclinical models of human metabolic function would be topics of great interest.

Another potentially important area for denervation research is in the management of intractable pain. Denervation therapy for pain management has been described using both surgical and percutaneous techniques. Celiac ganglion block is an example of a widely applied percutaneous chemolytic denervation technique performed in patients with intractable abdominal pain, usually secondary to intraabdominal malignancy. The same result may be obtained more easily and perhaps more safely through a transvascular route or by using low-intensity focused US or high-intensity focused US. If effective, the benefits of these procedures could be extended to patients with more common conditions such as chronic pancreatitis.

The encouraging results of RDN studies have reawakened interest in minimally invasive modulation of sympathetic nerves. These nerves frequently travel along the vascular tracts, allowing nonsurgical access to these fibers. However, the focus on "denervation" has missed half of the opportunity—that is, minimally invasive nerve stimulation. The attraction of nerve destruction over stimulation is that the former can potentially be permanent and achieved in a single procedure, whereas stimulation would require a more permanent source to allow for recurring therapy. However, the concept of perivascular sympathetic nerve stimulation may be a future direction of investigation and technology innovation.

There may also be a potential to treat pulmonary HTN with denervation. Lastly, there are likely other metabolically active organs that may respond to denervation and result in a beneficial effect.

Panel Research Prioritization Recommendations

From these presentations, the panel comments, and insight provided by individuals present from industry and governmental agencies, a second round-robin discussion of the gaps in the medical knowledge about denervation was undertaken. The panel also considered the established SIR Foundation research consensus assessment guidelines: clinical importance, feasibility, translatable to practice in a reasonable period of time, degree of innovation, and importance to the goals of interventional radiologists. The dialogue led to a list of potential research initiatives. The **Table** provides a consolidated list of the priority areas for potential study developed by the panelists. The panel divided this list into preclinical, clinical, and translational levels of research.

The panel consensus recommended developing a MR imaging protocol to measure renal perfusion to and diffusion of the kidneys before and after RDN. A substudy of functional MR imaging of the brain to try to develop a better understanding of the central effects of RDN was also recommended.

Table. Priority Areas for Potential Study

Preclinical Studies	Clinical Trials for RDN	Preclinical Nonrenal Applications
Assess anatomic changes in perirenal afferent and efferent fibers with denervation	Define medication protocols in denervation trials to determine indications, measure responses, and determine clinical outcomes better	Glucose, glycogen, and lipid metabolism in denervation of the liver
Measure sympathetic activity in real time before, during, and after denervation	MR imaging measures of renovascular resistance, perfusion- and diffusion-weighted images, and functional MR imaging of the brain, with long-term follow up, after denervation	Glucose, glycogen, and lipid metabolism in denervation of the pancreas
Evaluate parasympathetic activity after RDN	Noninvasive imaging (eg, PET) of sympathetic activity in the kidney, heart, and brain with denervation	Denervation of splanchnic bed to decrease risk of acute decompensation in heart failure patients
Evaluate central autonomic balance in resistant hypertension and after RDN	Determine if RDN has any effect on arrhythmias independent of reducing BP with trial of denervation in patients with and without atrial fibrillation	Determine if there are differences in sympathetic tone, glucose metabolism, or lipids in liver transplant and kidney transplant patients compared with nontransplant patients
Develop a catheter-based technology to determine renal blood flow and resistance at the time of denervation	Assess potential for preconditioning of patients to optimize treatment response (eg, medications, salt intake, other factors)	
Investigate high- or low-intensity focused US of carotid body	Measure time dependency, vagal sympathetic response, and kidney function after denervation	
High-intensity focused US of a central focus (brain) for control of sympathetic tone	Noninvasive measurement of renal perfusion and vascular resistance before and after RDN	
MR imaging or US temperature mapping and monitoring during high- or low-intensity focused US RDN		
Real-time and long-term predictive imaging of effect of ablation		

BP = blood pressure; MR = magnetic resonance; PET = positron emission tomography; RDN = renal denervation; US = ultrasound.

DISCUSSION

Pharmacologic management remains the "gold standard" for resistant HTN with which invasive therapies, such as RDN, ultimately must be compared. Although there are now randomized trial data demonstrating the beneficial effect of RDN in patients with resistant HTN, many questions about RDN, as compared with conventional pharmacologic therapy, have not been addressed. Beyond measuring change in systolic BP, the RCP reached consensus that RDN must be compared with best medical therapy for quality of life, long-term risk and benefit in regard to renal and cardiovascular outcomes, costs, ability of patients to stop taking some medications, incidence of early and late complications, and subpopulation of patients that are most likely to benefit from RDN (76).

To date, RDN clinical trials have focused on patients with resistant HTN, with systolic BPs > 160-165 mm Hg on ambulatory BP monitoring (9,36). Several subpopulations are now being studied, and one subpopulation of particular interest comprises subjects having systolic BPs measuring 140–160 mm Hg. Age, weight, gender, ethnicity, glucose intolerance, diabetes mellitus, renal artery stenosis, and renal insufficiency are additional potentially important variables for assessment. Multiple studies are underway to evaluate the effect of RDN on heart failure and tachyarrhythmias. Randomized controlled studies with evaluation of these subgroups become even more important as RDN is applied in an off-label application to other indications beyond resistant HTN.

In choosing among potential areas of clinical research focus, the appropriate priority order for investigation

should consider the size of the study population, the potential clinical impact of the study, and the results of ongoing preclinical and clinical studies that would help define the mechanism and effect of RDN. The RCP believed that measurements of changes in renal and global sympathetic activity using MR imaging techniques to measure renal perfusion and vascular resistance were of high importance (81). Although these MR imaging techniques lack quantitative confirmation, they do provide a reasonable approximation of renal perfusion and renal resistance. Although direct imaging of the sympathetic nerves is not possible at the present time, imaging of the brain using functional MR imaging techniques may be a useful substudy to assess for changes in central autonomic activity after RDN. There may also be a potential role for optical coherence tomography to assess changes in the renal artery endothelium, catheter-based electrophysiologic measurements, or molecular imaging to define better the multitude of potential effects of RDN.

The panel had strong opinions about recommending preclinical studies in several additional areas. Jordan et al (19) pointed out the need for basic information on sympathetic changes after RDN. The panel recommendations include PET imaging of sympathetic activity in the kidney and heart and possibly the brain. NE analogues have been approved for human use (82), but their use in the kidneys is unproven. There was also general consensus that preclinical investigation of denervation in other organs should be a priority. There is a long history of percutaneous injections for pain management (83), but sympathetic and parasympathetic inhibition by percutaneous chemical injection is largely unexplored for other indications. Similarly, percutaneous ablation of renal nerves should also be examined as an alternative to endovascular ablation.

Other organizations and ad hoc committees have endeavored to form consensus reports on research initiatives and clinical trial design (84,85). Similar to those reports, this consensus report is based on the consensus of a small group that may not represent the opinion of a larger group of experts in this field. Despite highly significant reductions in BP, few patients are able to change their antihypertensive medication profile substantially after RDN, and the number of medications may actually be increased. This finding raises questions about quality of life and economic issues that were not addressed by the previous clinical studies or this panel. These proceedings are limited by access to the latest data in this very rapidly evolving field. Nevertheless, the consensus from this panel provides an additional roadmap for protocol development.

In conclusion, pharmacologic and minimally invasive therapies for resistant HTN have entered a new era. Important clinical questions remain about the definition of resistant HTN, the identification of optimal target populations, appropriate measurement of outcomes, and potential subpopulations and alternative indications for denervation therapy. Measurement of renal sympathetic activity or, indirectly, changes in renovascular resistance presents a useful focus for clinical research in RDN and was the consensus of this panel of experts. Equally important is the need for preclinical research in quantitative measurement of sympathetic activity in the kidney and the evaluation of other abdominal visceral applications of denervation.

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