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Renal Sympathetic Denervation Using an Irrigated Radiofrequency Ablation Catheter for the Management of Drug-Resistant Hypertension

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Objectives This study sought to assess whether renal sympathetic denervation (RSDN) can be achieved using an off-the-shelf saline-irrigated radiofrequency ablation (RFA) catheter typically employed for cardiac tissue ablation.

Background RSDN using a specialized solid-tip RFA catheter has recently been demonstrated to safely reduce systemic blood pressure in patients with refractory hypertension. For cardiac tissue ablation, RFA technology has evolved from nonirrigated to saline-irrigated ablation electrodes to improve both safety and effectiveness.

Methods Ten patients with resistant hypertension underwent renal angiography, followed by bilateral RSDN with a saline-irrigated RFA catheter. Ambulatory blood pressure recordings (24 h) were obtained at baseline, 1, 3, and 6 months after the procedure. Repeat renal angiography was performed during follow-up to assess for arterial stenosis or aneurysm. In 5 patients, pre- and post-procedural serum measures of renal function and sympathetic activity were obtained: aldosterone; metanephrine; normetanephrine; plasma renin activity; and creatinine.

Results Over a 6-month period: 1) the systolic/diastolic blood pressure decreased by −21/−11 mm Hg; 2) all patients experienced a decrease in systolic blood pressure of at least 10 mm Hg (range 10 to 40 mm Hg); 3) there was no evidence of renal artery stenosis or aneurysm at repeat angiography; and 4) there was a significant decrease in metanephrine (−12 ± 4, $p = 0.003$), normetanephrine (−18 ± 4, $p = 0.0008$), and aldosterone levels (−60 ± 33 ng/l, $p = 0.02$) at 3 months. There was no significant change in plasma renin activity (−0.2 mg/l/hod, $p = 0.4$). There was no significant change in serum creatinine (−1 mmol/l, $p = 0.4$).

Conclusions These data provide the proof-of-principle that RSDN can be performed using an off-the-shelf saline-irrigated RFA catheter. (J Am Coll Cardiol Intv 2012;5:758–65) © 2012 by the American College of Cardiology Foundation

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Despite the development of antihypertensive drugs designed to block various avenues of the complex renal-cardiovascular circuit, hypertension remains a considerable, and poorly managed, medical, social, and economic burden (1). For various reasons, including the considerable costs of treatment, up to 65% of hypertensive patients have untreated and/or uncontrolled blood pressure (BP). Of those, ~10% have resistant hypertension—defined as elevated BP refractory to treatment with ≥3 antihypertensive agents of different classes.

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From a pathophysiological perspective, in essential hypertension there is increased sympathetic drive from the kidneys, as measured by increased afferent firing of renal sympathetic nerves, as well as an increased rate of renal and whole-body norepinephrine spillover (2,3). Increased sympathetic nervous system (SNS) efference to the renal system, in turn, promotes Na+ reabsorption via nephritic alpha$_1$ adrenoreceptors and activation of the renin-angiotensin-aldosterone system—ultimately leading to volume expansion resulting in sustained elevations in systemic BP. Based in part on the surgical experience from over a half-century ago that thoracolumbar sympathectomy could normalize BP in patients with malignant hypertension (4,5), the Symplicity HTN (Renal Sympathetic Denervation in Patients with Treatment-Resistant Hypertension) trials recently demonstrated that the sympathetic nerve fibers along the renal arterial vasculature can be targeted for catheter ablation using a specialized radiofrequency ablation (RFA) catheter (6–8). Although spurring a great deal of scientific and clinical excitement, 2 important limitations of this approach are: 1) this specialized first-generation catheter for renal sympathetic denervation (RSDN) is a solid-tip RFA catheter that, in theory, may promote char formation; and 2) the specialized catheter used in this study is not yet commercially available in many countries.

By contrast, there is now over a decade of pre-clinical and clinical experience with the use of saline-irrigated RFA catheters for the ablation of cardiac arrhythmias. In theory, saline-irrigation has the advantage of being less likely to cause thrombus/char formation at the ablation site (9,10). Furthermore, saline irrigation is known to project ablation lesions to deeper within the tissue—a potential advantage during RSDN, given the adventitial location of the renal sympathetic nerves. Although these saline-irrigated RFA catheters have been employed widely in the ablation of cardiac chambers and the great vessels (e.g., aorta, pulmonary artery, pulmonary veins), there are no published data on the safety and efficacy of RSDN with off-the-shelf RFA catheters.

Methods

All procedures were performed after obtaining written informed consent according to the institutional guidelines at Homolka Hospital, Prague, Czech Republic.

Patient characteristics. This first-in-man clinical experience with a saline-irrigated RFA catheter for RSDN occurred in patients with a history of chronic hypertension (systolic BP ≥140 mm Hg) refractory to ≥3 antihypertensive medications (including at least 1 diuretic). Patients were excluded if they had a known secondary cause of hypertension, estimated glomerular filtration rate <45 ml/min, type 1 diabetes or known renovascular abnormalities (renal artery stenosis, previous renal artery stenting or angioplasty).

Baseline measurements. Because of the well-described phenomenon of "white coat hypertension," all patients underwent 24-h ambulatory blood pressure monitoring (ABPM) with an oscillometric device that obtained BP readings every 30 min during the day and every 60 min at night. In addition, before the delivery of any radiofrequency energy, the following baseline measurements were obtained from all patients: 1) serum creatinine; 2) plasma renin activity; 3) aldosterone; 4) metanephrine; and 5) normetanephrine.

Abbreviations and Acronyms

ABPM = ambulatory blood pressure monitoring
BP = blood pressure
RFA = radiofrequency ablation
RSDN = renal sympathetic denervation
SNS = sympathetic nervous system

Renal sympathetic denervation. Procedures were performed under either deep sedation or general anesthesia. After standard femoral vascular access, a pigtail catheter was advanced to the abdominal aorta, and contrast angiography was performed to localize and assess the renal arteries for accessibility and appropriateness for RSDN. An appropriate anatomy was one in which the renal arteries were identified, the takeoff of each renal artery from the aorta was amenable to catheter cannulation, and there was no significant observable renal arterial atherosclerosis where ablation would be performed.

Once the anatomy was deemed acceptable, a 3.5-mm-tip internally irrigated RFA catheter (Celcius Thermocool, Biosense Webster, Diamond Bar, California) was advanced under fluoroscopic guidance. A flexible 45-cm, 8-F sheath (Arrow International, Inc., Reading, Pennsylvania) was advanced over the ablation catheter to engage the renal artery ostium and allow for contrast visualization of the renal artery during catheter manipulation. The ablation catheter was then maneuvered within the renal artery to allow energy delivery in a circumferential, longitudinally staggered manner to minimize the chance of renal artery stenosis. Energy titration was performed to achieve a 10% to 20% drop in impedance at each location (11). No more than

Table 1. Baseline Patient Characteristics (N = 10)

Demographic information	
Age, yrs	61 ± 12
Men, %	80
Body mass index, kg/m^2	33 ± 5
Relevant medical history	
Hypertension	10 (100%)
Diabetes mellitus	3 (30%)
Atrial fibrillation	1 (10%)
CAD	2 (20%)
Obesity	8 (80%)
Dyslipidemia	6 (60%)
Antihypertensive drugs	
ACE inhibitor	10 (100%)
Angiotensin receptor blocker	8 (80%)
Beta-blocker	8 (80%)
Calcium-channel blocker	9 (90%)
Diuretic	10 (100%)
Centrally acting antihypertensive	10 (100%)

Values are mean ± SD or n (%).
ACE = angiotensin-converting enzyme; CAD = coronary artery disease.

7 ablation lesions, lasting 30 to 90 s each, were placed within each renal artery.

Follow-up. All patients underwent follow-up renal angiography to assess for renal artery stenosis. At this time, 5 patients additionally underwent repeat blood draws to measure serum creatinine, plasma renin activity, aldosterone, metanephrine, and normetanephrine. Additionally, all patients underwent: 1) repeat 24-h ABPM; and 2) were seen in the office at 1, 3, and 6 months post-procedure for assessment of adverse events and medication changes.

Statistical analysis. Continuous variables are expressed as mean ± SD. Descriptive statistics were applied to assess the major endpoints: 1) change in BP, as obtained from ABPM; 2) freedom from procedural complications; 3) a decrease in renal SNS breakdown products; and 4) freedom from change in renal function, as measured by serum creatinine levels.

Results

Patient characteristics. This prospective, consecutive series consisted of 10 hypertensive patients refractory to treatment with 6.7 ± 1 medications (range 4 to 9), including diuretic therapy. The mean age of the patient cohort was 61 ± 12 years; the mean body mass index was 33.2 ± 5 kg/m^2 (range 26.9 to 46.2 kg/m^2) (Table 1).

Ablation procedure. Renal angiography revealed a highly variable and often tortuous arterial anatomy. Nevertheless, the vasculature was amenable to ablation in all patients; in 1 patient, ablation was limited to 1 lesion within the right renal artery because of the presence of atherosclerosis. There was no pre-existing renal artery stenosis in any patient.

In the patient cohort, 91 ablation lesions were delivered. Overall, 5 ± 1 (range 2 to 6) and 4 ± 2 (range 1 to 7) lesions were delivered to the left and right renal artery, respectively (Table 2). The mean duration of ablation was 242 ± 98 s of RFA per patient (range 117 to 390 s). See Table 2 for a detailed account of ablation parameters and fluoroscopy duration/exposure. During radiofrequency energy delivery, pain was universally experienced; this discomfort lasted only the duration of ablation and was managed successfully with intravenous benzodiazepines or propofol.

Safety. There were no acute procedural adverse events. However, there were several instances of ablation-related luminal arterial irregularities—presumably renal arterial spasm; how-

Table 2. Procedural Characteristics

Patient #	No. of Lesions		Avg. Lesion Duration (s)	Total RF (s)	Temp. Max. (°C)	Power Avg. (W)	Power Max. (W)	Start Impedance (Ω)	Mean Impedance Δ (Ω)	Fluoroscopy Time (min)	Radiation Exposure (μGym^2)
	LRA	RRA									
1	5	6	30	333	37	15	17	163	9	23	10,301
2	4	4	15	117	36	17	20	159	18	19	8,306
3	4	4	21	169	42	12	13	171	10	9	5,487
4	5	1	24	145	37	17	19	217	24	12	8,883
5	6	5	30	328	43	10	12	159	10	10	4,639
6	6	7	30	390	37	15	16	201	16	13	6,641
7	2	3	24	149	39	14	16	172	11	18	7,876
8	6	5	30	330	40	11	13	206	23	8	2,785
9	6	4	25	254	37	13	15	246	18	14	4,288
10	4	4	25	203	35	18	20	221	24	15	9,482
Average	5 ± 1	4 ± 2	26 ± 6	242 ± 98	39 ± 3	15 ± 3	17 ± 3	192 ± 31	16 ± 6	14 ± 5	6,869 ± 2,495
Minimum	2	1	15	117	35	10	13	159	9	8	2,785
Maximum	6	7	30	390	43	18	20	246	24	23	10,301

LRA = left renal artery; RF = radiofrequency; RRA = right renal artery; Temp. = temperature.

ever, none of these was flow-limiting. When encountered, intra-arterial nitroglycerin was typically administered. All patients were discharged within 24 h of the procedure. During repeat renal angiography at 3 months after the procedure, there were no instances of renal arterial narrowing or stenosis or aneurysmal dilation; indeed, there were not even any instances of luminal irregularities. All patients were free from adverse events. As determined by baseline and 3-month serum creatinine levels, there was also no significant change in renal function (71 ± 20 ng/l vs. 70 ± 16 μmol/l, respectively: Δ = −1 mmol/l, p = 0.4).

Blood pressure. As determined by 24-h ABPM, the mean baseline BP was 158 ± 16/88 ± 15 mm Hg on 6.7 ± 1 antihypertensive medications (range 4 to 9). All patients were taking at least 1 diuretic and at least 1 centrally acting antihypertensive drug; additionally, 8 patients were taking an angiotensin-converting enzyme -inhibitor, 8 an angiotensin receptor blocker, 7 a beta-blocker, and 8 a calcium-channel blocker.

During repeat 24-h ABPM at 1, 3, and 6 months after the procedure, significant changes from baseline were observed at all time points (Figs. 1 and 2). At 1 month, the mean BP was 152 ± 14/83 ± 13 mm Hg, indicating a change of −6 ± 4 mm Hg in systolic BP (range −1 to −15 mm Hg; p = 0.002) and −4 ± 5 mm Hg (range 5 to −12 mm Hg; p = 0.02) in diastolic BP. BP changes were more dramatic at 3 months: the BP was 136 ± 12/75 ± 13 mm Hg, indicating a change from baseline of −22 ± 11 mm Hg in systolic BP (range −27 to −40 mm Hg; p = 0.0001) and −13 ± 6 mm Hg (range −4 to −27 mm Hg; p = 0.0001) in diastolic BP. These BP changes were sustained at 6 months. The BP was 135 ± 8/76 ± 8 mm Hg, indicating a change from baseline of −21 ± 15 mm Hg in systolic BP (range −10 to −40 mm Hg; p = 0.003) and −11 ± 9 mm Hg (range 0 to −26 mm Hg; p = 0.005) in diastolic BP. On a per-patient basis, significant (≥10 mm Hg) decreases in systolic BP were observed in all patients.

By 6 months, because of sustained decreases in systemic BP, all patients were able to decrease the dosage of at least 1 medication. In addition, 9 of 10 patients discontinued at least 1 medication altogether (mean number of drugs at 6 months: 5 ± 1 drug; range 3 to 6). By contrast, despite significant decreases in BP, all 10 patients continued on antihypertensive therapy at 6 months, including diuretics in all patients, centrally acting antihypertensive drugs in 9 patients, angiotensin-converting enzyme inhibitors in 8 patients, angiotensin receptor blockers in 6 patients, beta-blockers in 6 patients, and calcium-channel blockers in 6 patients (Fig. 3).

Renal and sympathetic hormone activity. Five patients underwent baseline and 3-month blood sampling for renal hormones. A significant decrease was observed in the levels of SNS metabolites, including metanephrines (Δ = −12 ± 4, p = 0.003) and normetanephrines (Δ = −18 ± 4, p = 0.0008) (Table 3). There was also a significant decrease in aldosterone levels (Δ = −60 ± 33 ng/l, p = 0.02). Changes

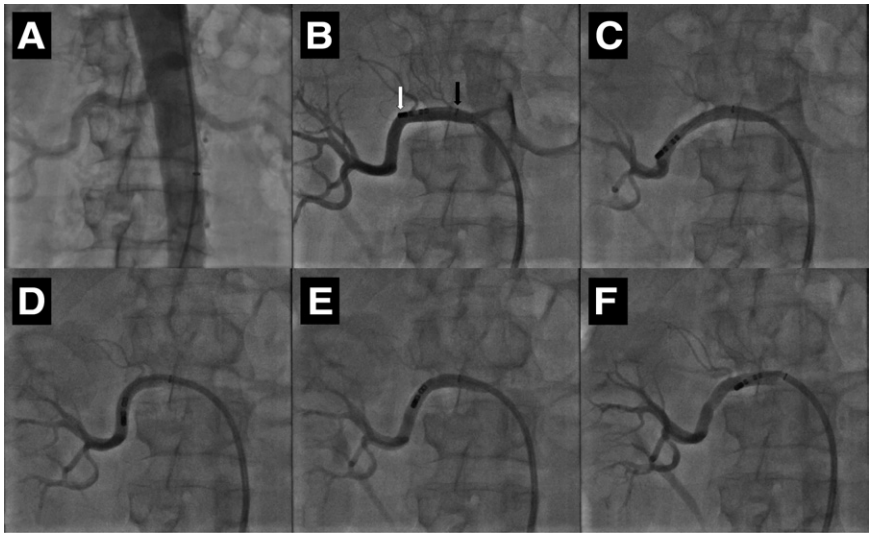

Figure 1. Catheter Positioning During Renal Sympathetic Denervation

(A) Contrast injection into the abdominal aorta identifies the locations and number of renal arteries. **(B)** With the saline-irrigated radiofrequency ablation catheter (**white arrow** at tip) placed within the right renal artery, the vascular sheath (**black arrow** at tip) is advanced over the catheter into the artery, and contrast is injected to visualize the vessel. Then, the catheter is serially positioned along the superior **(C),** anterior **(D),** posterior **(E)**, and inferior **(F)** aspects of the right renal artery to deliver radiofrequency energy.

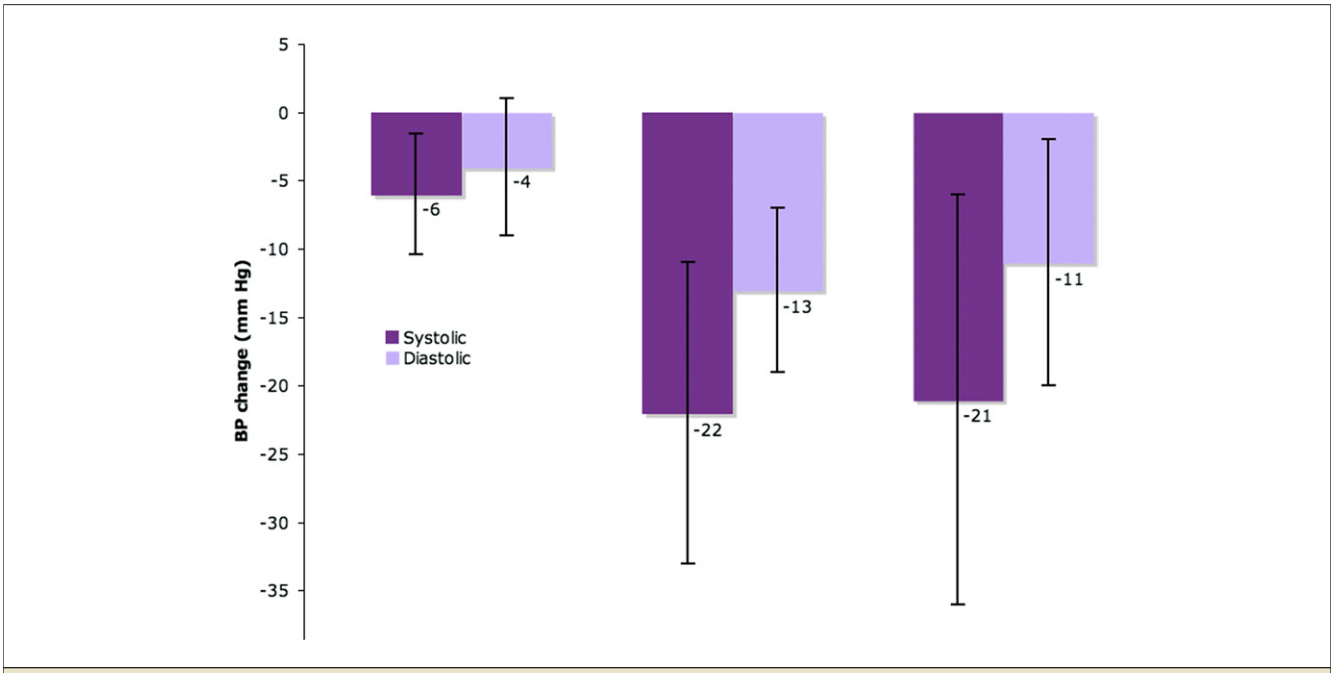

Figure 2. Cohort BP Changes From Baseline at 1, 3, and 6 Months

Shown are the decreases in mean systolic and diastolic blood pressure (BP), as determined by 24-h ambulatory blood pressure monitoring at 1, 3, and 6 months, As compared to baseline, the decrease in systolic/diastolic BP at 1, 3, and 6 months were −6 ± 4/−4 ± 5 mm Hg, −22 ± 11/−13 ± 6 mm Hg, and −21 ± 15/−11 ± 9 mm Hg, respectively.

in the plasma renin activity were not significant: ($\Delta = -0.2$ mg/l/hod, $p = 0.4$).

Discussion

This study demonstrated that renal sympathetic denervation with an externally irrigated RFA catheter is both safe and effective in a series of patients with drug-resistant, systemic hypertension. In addition to no acute procedural complications, repeat angiography at 3 months following ablation indicated the absence of renal arterial stenosis in all patients. As determined by 24-h ABPM, significant (≥10 mm Hg) decreases in systolic BP occurred in all patients at 6 months. In the total patient cohort, a statistically significant decrease was observed in systemic BP at 1, 3, and 6 months after the procedure, along with concurrent, statistically significant decreases in blood levels of renal hormones—metanephrines, normetanephrines, and aldosterone.

Previous studies. The initial clinical studies demonstrating the proof-of-principle that catheter-based RSDN can significantly decrease the BP in patients with refractory hypertension were performed using a specialized solid-tip RFA catheter (7,8). The first, Symplicity HTN-1, was a nonrandomized study employing this specialized RFA catheter in 45 drug-resistant hypertensive patients; the baseline office BP (177 ± 20 mm Hg/101 ± 15 mm Hg, on 4.7 antihypertensive medications) decreased by a mean of 27/17 mm Hg at 1 year. There was both a concurrent 47% reduction in renal noradrenaline spillover and a 66% decrease in muscle SNS activity. Most importantly, this favorable BP decrease was recently reported to be maintained over 2 years (8).

Symplicity HTN-2 also evaluated RSDN in patients with refractory hypertension, but this was a randomized clinical trial. In this study of 106 randomized patients, the 6-month office BP in the denervation group decreased by 32/12 mm Hg (baseline of 178/96 mm Hg, $p < 0.0001$), whereas they did not differ from baseline in the control group (change of 1/0 mm Hg, baseline 178/97 mm Hg, p = NS). From an individual perspective, 41 of 49 patients (84%) in the renal denervation group experienced a 6-month BP decrease of ≥10 mm Hg. Importantly, no serious procedure-related adverse events were noted.

Symplicity HTN-2 was limited by the absence of a true placebo control because patients were not blinded to their treatment assignment. However, both the magnitude of the relative clinical benefit observed in the RSDN group and the mechanistic data confirming the pathophysiological rationale for improved BP underlie the significant enthusiasm and optimism for the role of RSDN in refractory hypertension. Indeed, there is also significant scientific interest and active clinical investigation in the potential role for RSDN in other pathological states characterized by SNS overactivity, such as type 2 diabetes or metabolic syndrome, congestive heart failure, cardiac arrhythmias, and sleep apnea.

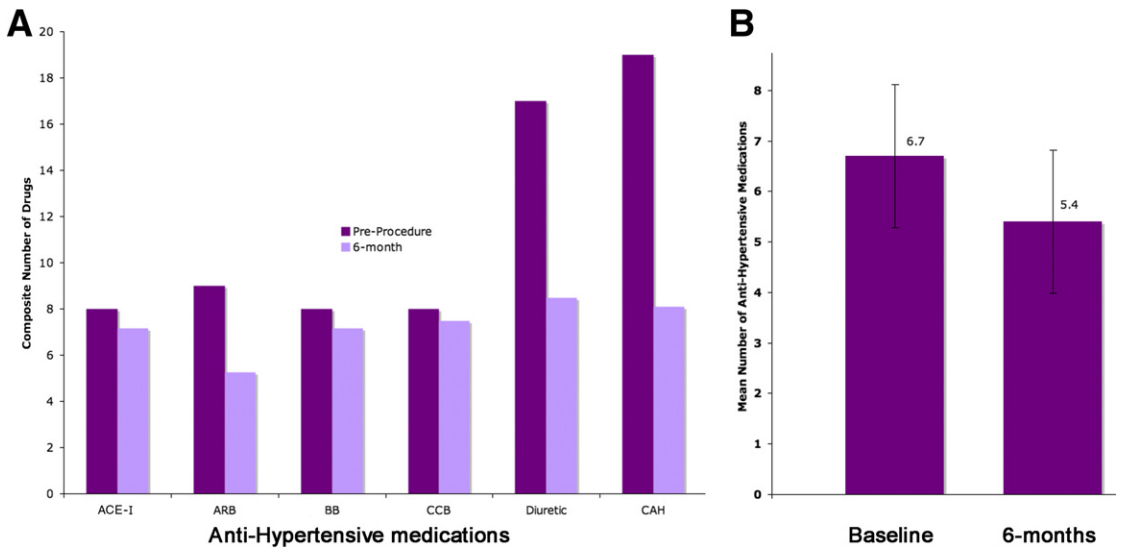

Figure 3. Antihypertensive Medications at Baseline and 6 Months After Procedure

(A) This chart indicates the mean number of antihypertensive medications for the patient cohort at baseline and 6 months; the mean number of drugs is displayed adjacent to the error bar. **(B)** This chart indicates the mean dose equivalent of antihypertensive medications, broken down by type of antihypertensive medication. This composite number reflects both the discontinuation of a drug, as well as a decrease in dosage. A dose decrease at 6 months was reflected as a fraction of the baseline dose; for example, the baseline dosage of 10 mg equals 1 U of drug so if the dose was decreased to 5 mg at 6 months, this counts as 0.5 U of drug. ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta-blocker; CAH = centrally acting antihypertensive; CCB = calcium-channel blocker.

Radiofrequency ablation technology. The specialized RFA catheter employed in the Symplicity HTN-1 and Symplicity HTN-2 trials was critical to establishing the feasibility and efficacy of catheter-based RSDN. But based on the wealth of experience in cardiac electrophysiology using radiofrequency energy to ablate cardiac arrhythmias, it would be best to view this solid-tip radiofrequency catheter as a first-generation ablation system for several reasons. First, with a solid-tip catheter, as energy is being delivered from the ablation electrode to the tissue, the heated tissue in turn heats the electrode with which it is in contact. This creates the potential for char formation on the electrode—the probability of which increases with increasing temperatures (9,10). Second, during radiofrequency energy delivery, heating is greatest at the tissue-electrode interface, which has a tendency to both limit the depth of the lesion and maximize the amount of damage to the endothelium.

Table 3. Average Measurements at Renal Sampling (n = 5)

	Pre	Post	Δ	p Value
Renin	0.8 ± 0.3	0.6 ± 0.4	−0.2 ± 0.6	0.40
Aldosterone	111 ± 40	52 ± 14	−60 ± 33	0.02
Metanephrine	36 ± 12	24 ± 9	−12 ± 4	0.003
Normetanephrine	67 ± 22	49 ± 21	−18 ± 4	0.0008

Values are mean ± SD.

Whereas temperature monitoring of the ablation electrode during solid-tip RFA can somewhat ameliorate some of these concerns, it is clear that the safest and most effective approach to radiofrequency energy delivery is with saline irrigation. By actively cooling the ablation electrode during RFA, it is possible to both increase the point of greatest heating to below the surface of the tissue and minimize the possibility of char formation because the temperature of the ablation electrode can be limited to <45°C by the saline irrigation. These advantages to saline irrigation are significant enough that most left-sided cardiac ablations are now performed using irrigated ablation catheters (10).

Because saline-irrigated RFA catheters specialized for RSDN procedures do not yet exist, we employed an off-the-shelf saline-irrigated electrophysiology ablation catheter for RSDN in this study. As expected, the amount of energy delivered is higher than was used with the specialized catheter because the size of the irrigated ablation electrode is significantly larger and in addition to cooling the ablation electrode, the saline carries some current away from the catheter. Accordingly, energy delivery using the irrigated catheter was titrated according to the level of impedance drop—a strategy almost universally employed during cardiac ablation—as the acute impedance drop during catheter ablation is a direct reflection to the magnitude of the volume of tissue being heated (11).

Even though other cardiovascular applications have elucidated the advantages of saline-irrigation over solid-tip ablation—minimization of surface damage with the concurrent creation of deeper lesions—it has not yet been proven that saline irrigation will improve the outcome in RSDN. Indeed, the high blood flow conditions of the renal arteries may allow adequate ambient cooling of the ablation electrode even with solid-tip nonirrigated ablation catheters. Also, a chronic porcine study of RSDN using a solid-tip radiofrequency energy catheter revealed no evidence of intimal hyperplasia after 6 months (12). By contrast, in the presence of atherosclerotic changes to the arterial wall, saline irrigation may be required to generate an adequate ablation lesion. Finally, though not seen in the present series, the 8-F puncture required for the saline-irrigated catheter is larger than the 6-F puncture needed for the solid-tip catheter used in the Symplicity trials and may potentiate more vascular access complications. Ultimately, the role of saline irrigation for radiofrequency-based RSDN should be explored further in randomized clinical trials.

Technical aspects of RSDN with the irrigated catheter. From a technical perspective, maneuvering the saline-irrigated RFA catheter into the renal arteries was somewhat difficult because of the often acute, inferior angle of takeoff of the renal arteries from the aorta. However, our data demonstrate that it is both possible and safe to employ this catheter to perform RSDN. This has been further verified in an additional 50+ patients (V. Reddy and P. Neuzil, personal communication, March 2012). By contrast, it is clear that a catheter system designed for renal arterial access, such as that employed in the Symplicity studies, is technically advantageous—though future RFA catheters will likely incorporate a saline-irrigated ablative element.

Procedural outcome. Whereas the limited number of patients precludes robust conclusions from this study, all 10 patients underwent RSDN with the saline-irrigated RFA catheter without any procedural complications. At 3 months after the procedure, there was no evidence of renal artery stenosis or aneurysm. Additional follow-up in a larger cohort of patients for a longer period is mandatory before definitively concluding this to be a safe approach for RSDN.

Similar to what was previously reported in the Symplicity HTN trials, the BP decrease from a baseline of 158 ± 16/88 ± 15 mm Hg was modest at 1 month (−6/−4 mm Hg, p = 0.002/p = 0.02), but decreased more significantly at 3 months (−22/−13 mm Hg, p = 0.0001/p = 0.0001). These blood pressure changes were sustained at 6 months (−21/−11 mm Hg, p = 0.003/p = 0.005). This progressive and sustained change indicates that the physiological effect of RSDN is not immediate, but as previously noted, requires a period of months to achieve its full effect. In addition, at least for 6 months, there was no evidence of reinnervation. This is consistent with prior data indicating an antihypertensive effect that persists for at least 2 years (8).

Regarding the magnitude of BP reduction, it is important to recognize that the primary means for assessing BP change in our study was 24-h ABPM. In Simplicity HTN-2, 24-h ABPM was available for 20 and 25 patients in the RSDN and control groups, respectively (8). It is interesting (though ultimately inconclusive) that the magnitude of BP reduction observed between baseline and 6 months in Simplicity HTN-2 (−11/−7 vs. −3/−1 mm Hg for the RSDN and controls, respectively) was directionally consistent, but numerically less than observed in the present study (−21/−11 mm Hg).

The mechanism for such a disparity could be related to: 1) differences in patient populations; 2) the ability of saline-irrigation to project ablative energy deeper in tissue; and 3) the larger electrode of the irrigated RFA catheter might allow for greater coverage of the vessel perimeter, thereby maximizing the effect of the RSDN procedure. This might also explain why all patients in the present series exhibited at least some BP drop—as compared to a 14% and 16% nonresponder rate in Symplicity HTN-1 and -2, respectively (6,7). However, both the small number of patients in the present study and the absence of a control group mandate that we consider these data as merely hypothesis generating and will ultimately require randomized clinical trial testing.

Venous sampling revealed significant decreases in metanephrine, normetanephrine, and aldosterone levels. Because metanephrine and normetanephrine are breakdown products of the neurotransmitters epinephrine and norepinephrine, their levels should decrease if kidney-central SNS axis is modified. These changes are consistent with prior observations of a decrease in renal and total body norepinephrine spillover and a decrease in muscle SNS activity (13). In addition, the observation that aldosterone levels are also statistically significantly decreased after RSDN is consistent with an important effect on the renin-angiotensin-aldosterone system. There was no statistically significant change in plasma renin activity, but this may be due to the small sample size. There were only a limited number of patients in our series. Though not technically feasible, it would have been preferable to determine the real-time rate of neurohormone production (i.e., norepinephrine spillover). Still, these data add to the current body of literature regarding the physiological impact of RSDN.

Study limitations. Despite observing a statistically significant BP reduction even with the relatively small number of patients included in this series, an important limitation of this study was the lack of a placebo control. It has been well described that when administering a placebo "treatment," the biofeedback pressure-lowering capability in hypertensive individuals is both real and powerful. Therefore, despite the concordance of our data with the Simplicity HTN studies, it is impossible to rule out with absolute certainty that the favorable effect on BP was not in part, or in whole, due to

the placebo effects of biofeedback. It is clear that a randomized controlled trial with a true placebo control, and ideally of double-blind design, will be necessary to definitively establish the efficacy of RSDN with the saline-irrigated RFA catheter in refractory hypertension. Indeed, until such definitive trials, we believe that procedures employing this catheter for off-label use are best performed in the setting of clinical registries.

Conclusions

RSDN can be performed safely and effectively in patients with resistant hypertension, using an off-the-shelf saline-irrigated RFA catheter. This feasibility experience provides the scientific basis for future randomized controlled trials to address both the scientific question of the safety and effectiveness of RSDN in refractory hypertensive patients in a placebo-controlled blinded manner and the technical question as to relative safety and efficacy of solid-tip and saline-irrigated RFA for RSDN.

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