INDIAN HEART JOURNAL 67 (2015) 207–213

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Original Article

Renal sympathetic denervation using an externally irrigated radiofrequency ablation catheter for treatment of resistant hypertension – Acute safety and short term efficacy

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ARTICLE INFO

Article history:
Received 11 April 2014
Accepted 13 February 2015
Available online 21 May 2015

Keywords:
Resistant hypertension
Renal denervation
Modified saline irrigated ablation catheter

ABSTRACT

Objectives: This study was conducted to assess the acute safety and short term efficacy of renal sympathetic denervation (RSDN) using solid tip radiofrequency ablation (RFA) catheter and saline irrigation through the renal guiding catheter to achieve effective denervation.

Background: RSDN using a specialized solid-tip RFA catheter has recently been demonstrated to safely reduce systemic blood pressure in patients with refractory hypertension, the limitation being inadequate power delivery in renal arteries. So, we used solid-tip RFA catheter along with saline irrigation for RSDN.

Methods: Nine patients with resistant hypertension underwent CT and conventional renal angiography, followed by bilateral or unilateral RSDN using 5F RFA catheter with saline irrigation through renal guiding catheter. Repeat renal angiography was performed at the end of the procedure. In all patients, pre- and post-procedure serum creatinine was measured.

Results: Over 1-month period: 1) the systolic/diastolic blood pressure decreased by −57 ± 20/−25 ± 7.5 mm Hg; 2) all patients experienced a decrease in systolic blood pressure of at least −36 mm Hg (range 36–98 mm Hg); 3) there was no evidence of renal artery injury immediate post-procedure. There was no significant change in serum creatinine level.

Conclusions: This data shows the acute procedural safety and short term efficacy of RSDN using modified externally irrigated solid tip RFA catheter.

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http://dx.doi.org/10.1016/j.ihj.2015.02.020

Hypertension is a significant growing global health issue. Current therapeutic strategies for this condition are mainly based on lifestyle interventions and pharmacological approaches. The rates of control of blood pressure and the therapeutic efforts to prevent their sequelae however remain unsatisfactory and additional options are required. Among patients with hypertension, there exists a subset who are unable to achieve adequate BP control despite the use of multiple medications and dietary and lifestyle modifications. These patients (termed —refractory or —resistant) are, by common definition, receiving >3 different classes of antihypertensive therapy, with one being a diuretic, and at maximal recommended or maximal tolerated doses.[1]

The estimates of resistant hypertension prevalence range from 13% to 30% among adults receiving drug treatment for hypertension.[2,3]These numbers reflect a serious global health challenge given the observation that with every 20/10-mm Hg increase in blood pressure, cardiovascular mortality doubles.[4] For such patients, treatment options are few. Device or procedure-based therapies have also been studied recently. One such approach involves a percutaneous, catheter-based renal sympathetic denervation procedure to disrupt renal afferent and efferent nerves using radiofrequency ablation.[4,5] There is evidence that resistant hypertension may, at least in part, be mediated by chronic activation of the sympathetic nervous system (SNS).[6]

Initial proof-of-concept studies have demonstrated both reductions in BP and evidence of organ-specific sympathetic denervation. Furthermore, the procedure was found to be both simple to perform and safe.[7,8] Symplicity HTN-2 which is a randomized controlled clinical trial of renal denervation in patients with treatment-resistant hypertension, showed a 33/11 mm Hg reduction of 6-month office BP compared with controls.[8] Follow up of patients for 24 months in Symplicity HTN 1 had shown that blood pressure reduction with RSDN is durable.[9] Symplicity 3 did not show a significant reduction of systolic blood pressure in patients with resistant hypertension 6 months after renal-artery denervation as compared with a sham control.[10]

During RSDN, a Symplicity catheter connected to a radiofrequency (RF) generator is used to cause sympathetic denervation which is achieved percutaneously through the lumen of the main renal artery. As we do not have access to this catheter, we used conventional 5F solid tip ablation catheter for RSDN. We observed the inadequate power (sometimes as low as 0–1 W) delivery and rise in local temperature during RSDN. The initial clinical studies (Symplicity1 and 2) which demonstrated the proof of principle and safety of RSDN, have surprisingly not mentioned the amount of power delivered during renal denervation. During temperature-controlled RF ablation, the tip temperature, tissue temperature, and lesion size are affected by the electrode–tissue contact and cooling effects resulting from blood flow. With good contact between catheter tip and tissue and low cooling of the catheter tip, the target temperature can be reached with little power, resulting in small lesions even though a high tip temperature is being measured. In contrast, a low tip temperature can be caused by a high level of convective cooling, which results in higher power delivery to reach the target temperature, yielding a larger lesion. Power delivery determines the size and depth of the RF lesion created.[11] Velocity of blood flow in renal arteries is normally fast but once the arteries are engaged with renal guide, the flow reduces resulting in inadequate cooling of the catheter–endothelial surface interface. As a result adequate power is not delivered to create a lesion in the vessel wall at the level of adventitia where nerve endings are located. Theoretically rise in temperature at catheter–endothelial surface interface can cause endothelial injury, thrombus formation and charring. Rise in local temperature will not allow adequate power and in turn temperature to be delivered to the deeper tissues, thereby creating inadequate RF lesion at adventitial layer. It can be avoided by using irrigation tip catheter but the size of available catheters is larger than 7.5F. Manipulating larger catheter in renal arteries may not only be difficult, but harmful. So, we used external cooling by irrigating through the renal guiding catheter as described below. We report here our experience with external cooling by saline irrigation through the renal guiding catheter using conventional solid tip radiofrequency ablation catheters in nine patients with RH.

1. Methods

Procedure was performed after obtaining written informed consent in all patients according to the institutional guidelines at Narayana Hrudayalaya Hospital, Bengaluru, India.

1.1. *Patient characteristics*

All patients were suffering from chronic resistant hypertension (systolic BP ≥140 mm Hg for more than 6 months) refractory to ≥3antihypertensive medications (including at least one diuretic). Patients with secondary hypertension, renal dysfunction not on dialysis and unsuitable renal artery anatomy (haemodynamically significant stenosis, post renal angioplasty, short and smaller renal arteries) were excluded.

1.2. *Baseline measurements*

All patients were observed for six months on appropriate antihypertensives to ensure that there is compliance with medications. Serum creatinine was measured in all patients. CT renal angiogram was done in all patients to look for renal artery diameter, length and stenosis.

1.3. *Renal sympathetic denervation*

Procedure was performed under conscious sedation and analgesia. After standard right femoral arterial access, heparin was administered to maintain ACT >250. 7F renal double curve (RDC, Medtronic Vascular Santa Rosa, CA, USA) guiding catheter was advanced over the 0.32 inch Terumo wire into the abdominal aorta. Each renal artery was selectively engaged and angiogram was performed to study the anatomy. Digital subtraction angiography (DSA) was performed to get a shadow of renal arteries. Under fluoroscopic guidance 5F, 4 mm solid tip ablation catheter (St. Jude Medical, St. Paul, Minnesota, USA) was advanced into distal renal artery (Fig. 1). A Stockert RF generator was used to deliver RF energy in

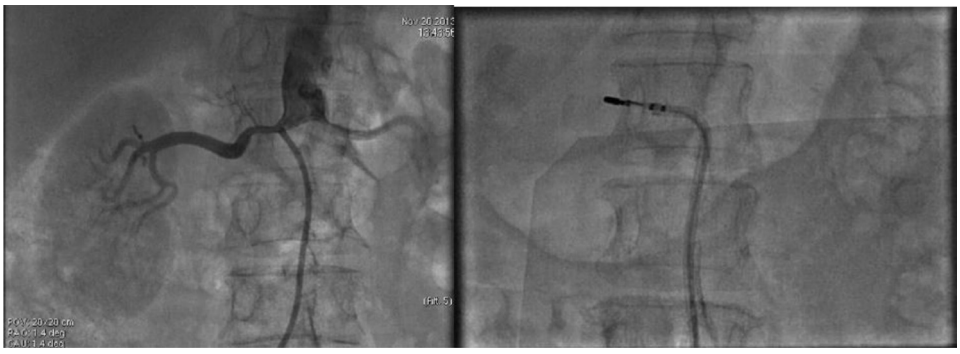

Fig. 1 – Renal angiogram and RFA catheter in the renal artery.

unipolar mode. RDC was attached to three port manifold through Y connector and 20 cc leur lock syringe filled with saline was attached to the manifold (Fig. 2). Irrigation was started manually just before delivering RF energy, maintaining sufficient saline flow to achieve 8–10 W power with temperature limit of 43 °C. RF energy was delivered for 30 s in each endothelial location after adequate power (8 W) was reached, targeting an impedance drop of 5–10 Ω. RFA was delivered in this manner at 5–6 locations (each separated by at least 5 mm) from distal to proximal, approximately in a circumferential manner. Post-procedure angiogram was done to look for dissection, spasm and blood flow.

1.4. *Follow up*

Post-procedure, all patients were being followed up for regular office blood pressure (7 days, 1 month, 3 months, 6 months and 1 year), and serum creatinine measurement.

1.5. *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 the office blood pressure; 2) freedom from procedural complications; and 3) freedom from change in renal function, as measured by serum creatinine levels.

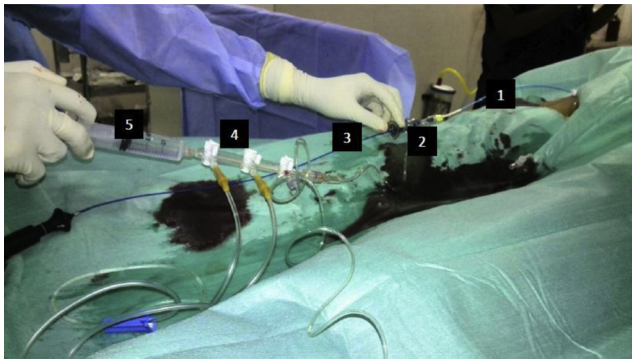

Fig. 2 – RFA catheter, renal guide, manifold and saline irrigation syringe assembly. 1 – Renal double curve guide; 2 – Y connector; 3 – 5F solid tip ablation catheter (St. Jude Medical, St. Paul, Minnesota, USA); 4 – Manifold; 5–20 cc syringe filled with saline used for irrigation.

2. Results

2.1. *Patient characteristics*

This prospective, consecutive series consisted of 9 hypertensive patients refractory to treatment with mean of 4.6 medications (range 3–6), including diuretic therapy. The mean age of the patient cohort was 58.7 years (Table 1). We present results of one month follow up.

2.2. *Ablation procedure*

Renal angiography revealed variable number and tortuous arterial anatomy. Despite variable anatomy, the vasculature was amenable to ablation in one but all patients. There was one patient with ostial 60% stenosis of right renal artery; ablation was not attempted in right renal artery to avoid the risk of atheroembolisation and dissection. A total of 98 lesions were delivered in this patient cohort. Overall, the total number of

Table 1 – Baseline characteristics.

	$n = 9$
Demographics	
Mean age in years (SD)	58.7 (12)
Males	44.4%
Mean body mass index (SD)	27.23 (3.2)
Co-morbid conditions	
Diabetes mellitus	8
Atrial fibrillation	3
Coronary artery disease	1
End stage renal disease	1
Antihypertensive drugs	
Angiotensin converting enzyme inhibitor	1
Angiotensin receptor blocker	7
Beta-blocker	8
Calcium-channel blocker	6
Diuretic	9
Centrally acting antihypertensive	8
Alpha blocker	2

SD = Standard Deviation.

lesions delivered were 5.11 ± 0.2 (range 5–6) and 5.22 ± 1.35 (range 0–7) to the left and right renal arteries, respectively (Table 2). The mean duration of ablation was 41.1 ± 3.45 s per lesion. During radiofrequency energy delivery, variable degree of pain was experienced by all subjects. This discomfort lasted only for the duration of ablation and was managed successfully with intravenous benzodiazepines and fentanyl.

2.3. Complications

There were no major complications. One patient had significant bradycardia during ablation on the left side and required pulses of RF delivery to avoid severe bradycardia.

2.4. Blood pressure

The mean baseline blood pressure was 193.5 ± 25 mm Hg on 4.6 ± 0.71 antihypertensive medications (range 3–6). Details of medications are listed in Table 3. There was significant blood pressure drop within 24 h of procedure, so that dose of at least one medication could be reduced at discharge except in one patient with CKD. Average duration of follow up was one month at the end of which mean BP was 136 ± 17.7/80.6 ± 6.4 mm Hg indicating a change of −57 ± 20 mm Hg in systolic BP (range −36 to −98 mm Hg; $p < 0.0002$) and −25 ± 7.5 mm Hg (range −12 to −40 mm Hg; $p < 0.0002$) in diastolic BP. As there was sustained drop in blood pressure at one month follow up, at least one medication was stopped (centrally acting drugs) and dosage of other medicines were reduced as necessary.

2.5. Additional benefits

one patient with atrial fibrillation had recurrent pulmonary edema requiring multiple hospitalizations. After RSDN, her ventricular rate was better controlled with similar medications and no hospitalization for pulmonary edema was required at the end of 3 months follow up period.

2.6. Serum creatinine

There was no change in serum creatinine levels at 7 days and 1 month follow up establishing the safety of the procedure on renal function.

3. Discussion

Our study, in a small group of patients with drug resistant systemic hypertension, demonstrated that renal sympathetic denervation is safe and effective, using modified externally irrigated solid tip RFA catheter. There were no acute or subacute major complications. One patient had significant bradycardia during ablation which returned to normal heart rate after stopping ablation. There was significant (136 ± 17.7/80.6 ± 6.4 mm Hg) reduction in office blood pressure in all patients at one month follow up.

First in human clinical studies have demonstrated that RSDN can significantly decrease BP in patients with resistant hypertension using specially designed RFA catheters.[6,7] 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 concurrent 47% reduction in renal noradrenaline spill over and a 66% decrease in muscle SNS activity. Most importantly, this favorable BP decrease was reported to be maintained over 2 years.[7,9]

Symplicity HTN-2 also evaluated RSDN in patients with refractory hypertension and 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.[8]

Symplicity 3[10] was randomized trial of renal denervation with sham controlled arm. A total of 535 patients underwent randomization. The mean (±SD) change in systolic blood pressure at 6 months was −14.13 ± 23.93 mm Hg in the denervation group as compared with −11.74 ± 25.94 mm Hg in the sham-procedure group ($p < 0.001$ for both comparisons of the change from baseline), for a difference of −2.39 mm Hg (95% confidence interval [CI], −6.89 to 2.12; $p = 0.26$ for superiority with a margin of 5 mm Hg). The change in 24-h ambulatory systolic blood pressure was −6.75 ± 15.11 mm Hg in the denervation group and −4.79 ± 17.25 mm Hg in the

Table 2 – Radiofrequency ablation parameters.

Patient No.	No of lesions		Ablation duration in sec Mean (SD)	Energy delivered (in Watts)	Maximum temperature (Degrees)
	LRA	RRA			
1	5	5	40 (6)	8	40
2	10[a]	5	45 (5.2)	10	39
3	5	5	35 (4.8)	10	37
4	6	7	45 (7)	10	41
5	5	0	45 (5.4)	8	38
6	5	6	40 (4)	10	36
7	5	5	45 (5.2)	10	40
8	5	7	35 (4)	10	38
9	5	7	40 (5.2)	8	42

[a] Had bifurcation of renal artery. Five lesions were delivered into each. LRA = Left renal artery, RRA = Right renal artery.

Table 3 – Comparison of pre and post renal sympathetic denervation blood pressure values and antihypertensive drug requirements.

Patient No.	Baseline SBP	Post RSDN SBP	Baseline DBP	Post RSDN DBP	Pre RSDN No of drugs	Post RSDN No of drugs
1	148	112	98	76	4	1
2	150	110	92	72	3	2
3	206	150	104	80	4	1
4	170	128	92	80	5	4
5	210	130	110	80	6	5
6	216	168	140	100	5	3
7	224	148	108	90	4	3
8	218	120	110	70	5	3
9	200	158	100	78	5	4

SBP = Systolic Blood Pressure; RSDN = Renal Sympathetic Denervation; DBP = Diastolic Blood Pressure.

sham-procedure group, for a difference of −1.96 mm Hg (95% CI, −4.97 to 1.06; $p = 0.98$ for superiority with a margin of 2 mm Hg). After Symplicity 3 enthusiasm for renal denervation has reduced. Reasons for the failure of the trial need to be further analyzed.

3.1. *Radiofrequency ablation biophysics*

Specialized catheters used in Symplicity HTN-1 and Symplicity HTN-2 trials were conventional solid tip catheters. At steady state, the lesion size is proportional to the temperature measured at the interface between the tissue and the electrode as well as to the RF power amplitude. By using higher powers and achieving higher tissue temperatures, the lesion size can be increased. However, once the peak tissue temperature exceeds the threshold of 100 °C, boiling of the plasma at the electrode–tissue interface can ensue. When boiling occurs, denatured serum proteins and charred tissue form a thin film that adhere to the electrode, forming an electrically insulating coagulum, which is accompanied by a sudden increase in electrical impedance preventing further current flow into the tissue and further heating.[12,13]

This rise in impedance can be prevented by convective cooling. The higher magnitude of power increases the depth of direct resistive heating and, in turn, increases the radius of the effective heat source. In addition, higher temperatures are achieved 3–4 mm below the surface, and the entire radial temperature curve is shifted to a higher temperature over greater tissue depths.

Electrode-tip cooling can be achieved passively or actively. Passive tip cooling occurs when the circulating blood flow cools the mass of the ablation electrode and cools the electrode–tissue interface. Active tip cooling can be realized with a closed or open perfused-tip system. In each case, circulating saline from an infusion pump actively cools the electrode tip and the opposing design infuses the saline through weep holes in the electrode into the bloodstream. Both designs are effective and result in larger lesions and greater procedure efficacy than standard RF catheter ablation. Theoretical advantages and disadvantages of open perfusion versus closed perfusion catheter designs are claimed by device manufacturers and their spokes people, but the lesions produced and the clinical efficacy and safety profiles of these competing designs are very comparable.[14–17]

The tip cooling or perfusion has the apparent advantage of reducing the prevalence of coagulum and char formation. These advantages to saline irrigation are significant enough that most left-sided cardiac ablations are now performed using irrigated ablation catheters.[18]

We have noticed that there was abrupt impedance rise and inadequate power delivery during RSDN using 5F, 4 mm solid tip catheter in spite of being high blood flow in renal arteries. Effective cooling of ablation catheter may be prevented by the reduced blood flow after engaging renal arteries with RDC guiding catheter. Available irrigation tip catheters are of larger size making them inconvenient to use and difficult to manipulate in the renal arteries. So, we used saline irrigation manually through the renal guiding catheter and the power delivered is likely to be higher than non-irrigated solid tip specialized catheters used in trials.

There is a small prospective study ($n = 10$)[19] which demonstrated the safety and efficacy of irrigation tip ablation in RSDN. Renal angiography at 3 months showed no stenosis. There was better drop in BP in this study compared to 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, $p = 0.003/p = 0.005$). 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 this study (−21/−11 mm Hg).

SYMPLICITY HTN-3 trial, randomized, sham-controlled, blinded trial did not show a benefit of renal-artery denervation with respect to either of the efficacy end points for which the study was powered (reduction in office or ambulatory systolic blood pressure at 6 months).[10] This study lowered the enthusiasm for a promising breakthrough therapy in resistant hypertension. This led to the analysis of SYMPLICITY HTN-3 trial data. There is a learning curve for any procedure before getting optimal results. The enthusiasm to enroll more patients in a short duration of time increased the number of inexperienced operators. In this trial, procedure was performed by inexperienced operators as half of the operators performed only two procedures and 31% performed only one RDN procedure during the trial. Patients receiving more

ablation lesions showed greater reductions in blood pressure implying better denervation with more ablation.[20] Notching on angiography has been mentioned as confirmation of energy delivery by catheter. Notching can happen because of endothelial injury and spasm of vessel rather than trans mural energy delivery. As discussed above effective denervation needs adequate power delivery, which is unlikely to happen with solid tip catheter used in this trial. There is no data on the power delivered and impedance drop with each lesion. The set power needs to be delivered to achieve denervation. In our experience, power delivery cannot be achieved with solid tip catheter. We need to have irrigated tip catheters to ensure adequate power delivery and effective denervation. So, SYMPLICITY HTN-3 trial results need to be analyzed carefully before disregarding RSDN. There is a role for RSDN even in the event of failure of this major trial to demonstrate efficacy of renal denervation.

In our study, the magnitude of blood pressure reduction was higher compared to Symplicity trials and other studies. Blood pressure reduction was observed the very next day of RSDN. We had to reduce either the number or the dose of antihypertensive medications on discharge. The magnitude of blood pressure reduction in yet another study from Indian subcontinent is also more than (−43.5/21 mm Hg)[21] simplicity trials.

The reason for such a difference may be related to: 1) Racial difference 2) the ability of saline-irrigation to create better, deeper RF lesions and hence better denervation and 3) the larger electrode of the irrigated RFA catheter might allow for greater coverage of the vessel perimeter, thereby maximizing the effect of RSDN procedure. This might also explain why all patients in our series exhibited BP drop—as compared to a 14% and 16% non-responder rate in Symplicity HTN-1 and 2, respectively.[4,6] However, smaller number of patients in the present study and the absence of a control group, both mandate that we consider these data as merely hypothesis generating and understand that it will ultimately require randomized clinical trial testing.

4. Limitations

An important limitation of this study is that it is not a placebo controlled one. The blood pressure changes post RSDN is significant, which is unlikely to be related to pressure lowering biofeedback effect. We have not recorded ABPM at 1 month which is a second limitation. Yet another limitation is that we have not measured pre and post RSDN catecholamine levels.

4.1. *Conclusions*

RSDN can be performed safely and effectively in patients with resistant hypertension, using an off-the-label modified saline irrigated RFA catheter. This study experience provides the scientific basis for future randomized controlled trials to assess the safety and efficacy of RSDN with irrigated tip catheter targeting impedance drop, in refractory hypertensive patients in a placebo-controlled (sham procedure) blinded manner.

Conflicts of interest

All authors have none to declare.

Acknowledgments

We Thank Dr Sandeep Nair (research fellow at Cider Sinai, California, USA) and Manish Rai (research fellow at Cider Sinai, California) for giving valuable suggestions for manuscript preparation. We thank Mrs Gomathi Sundar for assisting with statistical analysis.

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