

Renal sympathetic denervation in the treatment of resistant hypertension

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SUMMARY

Hypertension is a significant cardiovascular risk factor. Although the mainstay of treatment remains medication, there are a number of patients with resistant hypertension who have elevated blood pressure despite multiple medications. Failure to achieve adequately controlled blood pressures despite medications put these patients at risk of target organ damage and significant morbidity from hypertension. The renal denervation procedure involves the application of radiofrequency energy or ultrasound at the renal arteries to modulate afferent and efferent sympathetic renal activity. This treatment potentially can improve blood pressure control in patients who have resistant hypertension despite medication. This article presents two case reports of successful treatment of resistant hypertension using radiofrequency renal sympathetic denervation (RDN) at a private medical centre using the latest Spyral catheter. We also reviewed the latest RDN trials to give some insights into this procedure.

INTRODUCTION

Hypertension is a significant cardiovascular risk factor that is implicated in coronary artery disease and stroke. Only about half of patients with hypertension are adequately controlled on medical therapy and about a quarter of patients may develop severe or resistant hypertension. Resistant hypertension is defined as failure to achieve target blood pressure (BP) of <140/90 mmHg while on full doses of an appropriate three-drug regimen that includes a diuretic.

Renal sympathetic denervation (RDN) was first used to treat resistant hypertension by modulating renal sympathetic nerve activity using radiofrequency ablation. Renal sympathetic efferent nerves activate the renin – angiotensin – aldosterone system, subsequently leading to a decrease renal blood flow, a decrease in urinary excretion of salt and water. By decreasing efferent sympathetic nerve activity, RDN can lower BP. This article presents two case reports of successful treatment of resistant hypertension using the latest Spyral catheter and we reviewed the latest RDN trials.

CASE REPORT

A 44-year-old man presented to an ophthalmologist at our centre, Subang Jaya Medical Centre, Malaysia for visual disturbance, diagnosed with right eye retinal artery occlusion and was found to have elevated blood pressure. The patient was referred to a cardiologist at our centre for further

management. The patient had no other medical history and was not on medication. His BP was 200/120 mmHg on initial consultation. He was started on amlodipine 10mg od, valsartan 160mg od, hydrochlorothiazide 25mg od.

After 4 weeks of treatment with medication, the patient still had an elevated office BP of 170/100 mmHg and hence, was admitted for further investigation. Investigations were performed to assess for target organ damage from hypertension and to rule out secondary causes of hypertension. Renal function was normal, creatinine was 84 $\mu\text{mol/l}$ with estimated glomerular filtration rate (eGFR) of >59 ml/min/1.73 m². Other normal results included Renin 10.1 (5.3-99 mU/L), Aldosterone 402 (103-1197 pmol/l), 24-hour urine Noradrenaline 214 (71-505 nmol/24 hr), urine Adrenaline 20 (9-122 nmol/24 hr), urine Dopamine 530 (0-3237 nmol/24 hr). Abdominal CT angiography showed no evidence of coarctation of aorta, renal artery stenosis and no adrenal masses. Echocardiography showed concentric left ventricular hypertrophy, with normal systolic function and no significant valve abnormalities. MRA of the brain showed, on diffusion weighted imaging, a few hyperintense foci in right corona radiata and left centrum semiovale, representing likely subacute infarction.

Despite treatment with the 3 hypertension medications and medication compliance monitored during hospital admission, 24-hour Ambulatory BP monitoring (ABPM) still showed severe systolic and diastolic hypertension and a non-dipper pattern (overall average: 171/105 mmHg). The patient was offered an option for further 4th medication or RDN procedure. He opted for RDN and consented for it.

The RDN procedure was performed under general anesthesia. After gaining vascular access via the right femoral artery, renal artery angiography was performed. Intravenous heparin was administered. Following catheterization and using the RDC guide catheter, a Symplicity® Spyral catheter (Medtronic, USA) was connected to a radiofrequency generator and inserted into each renal artery sequentially. The procedure was planned by identifying renal artery branches with sizes between 3 mm to 8 mm. Multiple applications of radiofrequency energy for up to 60s each were performed with 25 points ablated in the right and 28 points ablated in the left renal artery branches. There were no post-procedural complications, and the patient was discharged well with the continuation of the three hypertension medications.

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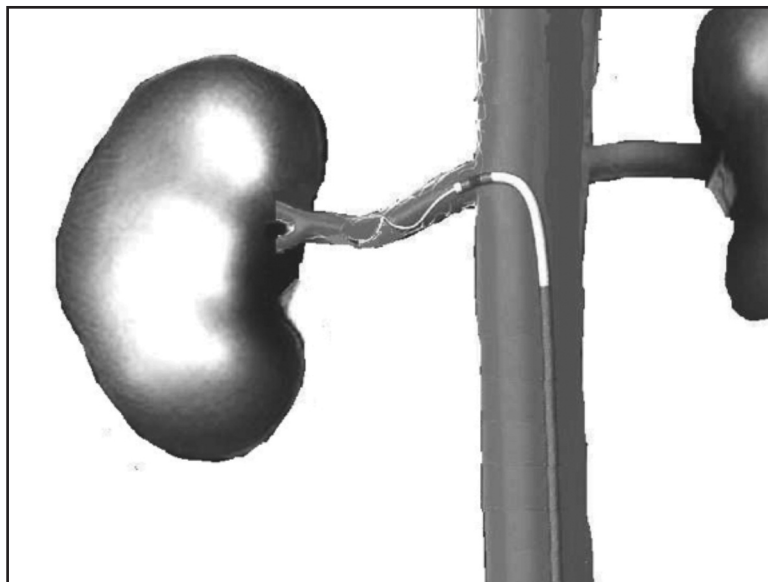


Fig. 1: The Spyrax catheter used for renal sympathetic denervation.

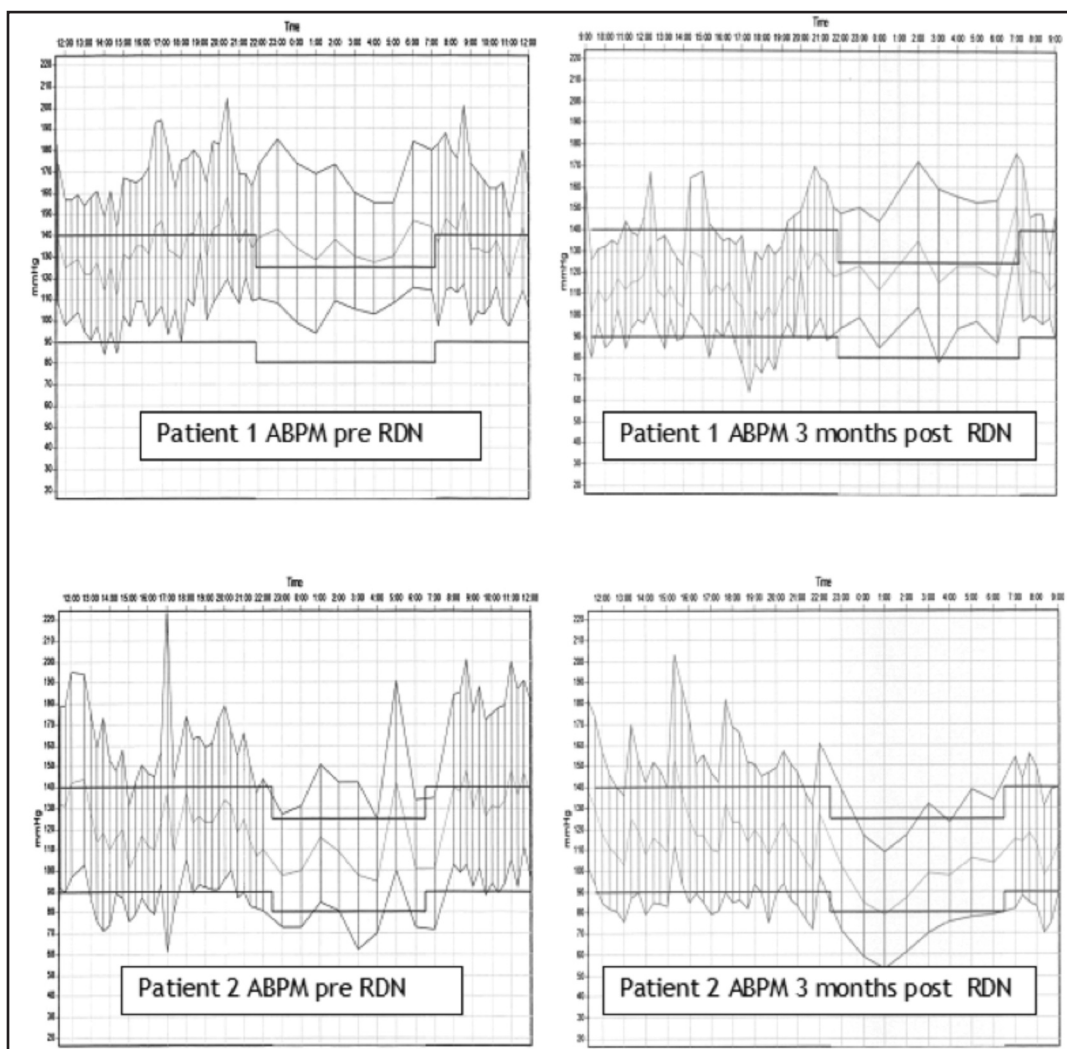


Fig. 2: Both patients demonstrated a significant reduction of BP with 24-hour ABPM at pre RDN procedure (left) and 3 months post procedure (right). For Patient 1 the mean BP decrease was 26/13 mmHg. For Patient 2 the mean BP decrease was 16/5 mmHg.

At one month follow up, renal function showed no significant deterioration with eGFR of >59 ml/min/1.73 m². There was sustained reduction of BP when 24-hour ABPM was repeat at 3 months (Figure 2). His 24-hour ABPM at 3 months after the procedure showed an average BP of 145/92 mmHg; (mean systolic and diastolic BP). At 3 months, the mean BP decrease was 26/13 mmHg (systolic and mean diastolic BP decrease). Further follow up for BP and renal imaging is planned.

CASE REPORT 2

A 69-year-old man, presented to the emergency department at our centre with symptoms of headache and lethargy. He had previous medical history of hypertension and diabetes mellitus. He was already on 5 hypertensive medications for more than a year, amlodipine 10mg od, co-provel (irbesartan/hydrochlorothiazide) 300 / 12.5mg od, bisoprolol 5mg od, physiotens 0.4 mg od. His BP was 180/100 mmHg on initial consultation.

He was admitted to the medical ward at our centre. Investigations were performed to rule out secondary causes of hypertension. Renal function was normal with creatinine 85 umol/l and estimated glomerular filtration rate (eGFR) of >59 ml/min/1.73 m². Other normal results included Renin 39.1(5.3-99 mU/L), Aldosterone 713 (103-1197 pmol/l), 24-hour urine Noradrenaline 340 (71-505 nmol/24 hr), urine Adrenaline 30 (9-122 nmol/24 hr), urine Dopamine 1636 (0-3237 nmol/24 hr). Abdominal CT angiography showed no evidence of coarctation of aorta, renal artery stenosis and no adrenal masses. Echocardiography showed normal left ventricular systolic function and no significant valve abnormalities.

Despite treatment with the five hypertension medications and medication compliance monitored during hospital admission, 24-hour ABPM still showed severe systolic and diastolic hypertension (overall average: 165/88 mmHg).

The patient agreed for the RDN procedure, he chose to have heavy sedation rather than general anesthesia during the procedure. Intravenous heparin was administered for the procedure. Following femoral arterial catheterization and using the RDC guide catheter, a Symplicity® Spyral catheter (Medtronic, USA) was inserted into each renal artery, connected to a radiofrequency generator. The procedure was planned by identifying renal artery branches with sizes between 3 mm to 8 mm. Multiple applications of radiofrequency energy for up to 60s each were performed with 24 points ablated in the right renal artery branches and 29 points ablated in the left renal artery branches. There were no post-procedural complications, and the patient was discharged well with the continuation of his hypertension medications.

At one month follow up, renal function showed no significant deterioration with eGFR of >59 ml/min/1.73 m². Follow up with the patient on the same doses of five BP medications showed office BP reduction and the patient felt symptomatically improved. There was BP reduction when 24-hour ABPM was repeated at 3 months (Figure 2). His 24-hour ABPM at 3 months after the procedure was overall average

149/83 mmHg. At 3 months, the mean BP decrease was 16/5 mmHg (systolic and mean diastolic BP decrease). Further follow-up for BP and renal imaging was planned.

DISCUSSION

These two cases illustrate the successful renal denervation treatment of resistant hypertension. Although the mainstay for the majority of hypertensive patients is still medication, there are a small proportion of patients who have persistent elevated blood pressure despite multiple medications for whom RDN may be helpful.

The first-generation radiofrequency ablation (RFA) system (Symplicity Flex; Medtronic, Minneapolis, Minnesota) used for RDN was a catheter with single electrode. The early study (SIMPLICITY HTN-1 study) using this studied 45 patients who underwent RDN treatment. The study demonstrated significant reduction in office systolic BP of 26 mmHg in the RDN group compared to 12 mmHg in the control group at 6 months.¹ The Symplicity HTN-2 trial,² a multicenter randomized controlled trial also showed success in lowering BP in hypertensive patients with ≥ 3 antihypertensive drugs. RDN was performed using the Symplicity Flex catheter. The study found that the mean office BP at 6 months dropped by 32 mmHg ($p < 0.001$) in the RDN group ($n = 52$) compared to BP drop of 12 mmHg in the control group ($n = 54$).

The Symplicity HTN-3 was a multicentre single blinded trial which randomised 535 patients on ≥ 3 antihypertensive medications to either RDN using Symplicity Flex or sham control.³ After 6 months following RDN treatment, there was a mean decrease in office systolic BP of 14.1 mm Hg in the RDN group ($n = 364$) compared to a decrease of 11.7 mm Hg in the control group ($n = 171$). Since both RDN and sham controlled groups showed significant decreases in the blood pressure, this raised doubt as to the genuine effectiveness of the RDN treatment.

Since the publication of SYMPPLICITY HTN-3 trial, further advances have been made in the technology for RDN. One such system, the Spyral catheter (Simplicity Spyral; Medtronic, Minneapolis, Minnesota) was designed as a 4-electrode system which for more effective ablation. The SPYRAL HTN-OFF MED and SPYRAL HTN-ON MED, were proof of concept studies for the Spyral catheter.^{4,5} The SPYRAL HTN-OFF MED showed that at 3 months following RDN, there was significant reduction in both office and 24-hour ambulatory BP from baseline in the treatment group (-10/-5.3 mmHg and -5.5/-4.8 mmHg) compared to the sham control group. Significant BP reduction in the RDN arm was also reported in the SPYRAL HTN-ON MED study at 6 months (-9.0/-6.0 mmHg for 24-hr ambulatory BP).

Several other randomized controlled trials have used RFA in renal denervation with variable results. The simplicity HTN-Japan trial included RDN ($n=22$) and control ($n=19$) subjects.⁶ The 6-month office SBP change was -16.6 ± 18.5 mmHg for RDN subjects ($P<0.001$) and -7.9 ± 21.0 mmHg for control subjects ($P=0.117$). The French DENER-HTN trial⁷ on patients with resistant hypertension found a mean change of systolic blood pressure at 6 months -15.8 mm Hg (95% CI -19.7 to

-11.9) in the renal denervation group and -9.9 mm Hg (95% CI -13.6 to -6.2) in the control group. A trial carried out in Denmark, the ReSet trial, randomized resistant hypertension patients to RDN ($n=36$) or a Sham procedure ($n=33$).⁸ This trial however, found no significant differences when comparing RDN to a sham procedure at 6 months [-6.1 ± 18.9 mmHg (RDN) vs. -4.3 ± 15.1 mmHg (SHAM)].

Apart from RFA as described above, catheter-based ablation of renal nerves has also been shown to be effective using ultrasound (Paradise ultrasound system; ReCor Medical, Palo Alto, California). The RADIANCE-HTN SOLO studied catheter-based ultrasound in patients who were not on antihypertensive medications.⁹ The decrease in daytime ambulatory systolic BP from baseline to 2 months was greater in the RSDN group (8.5 mmHg, $n = 74$) when compared to the sham group (2.2 mmHg, $n = 72$). Two additional RCTs with ultrasound-based ablation systems are ongoing.¹⁰ The RADIANCE-HTN TRIO trial is being conducted in the United States and Europe. The REQUIRE study is being conducted in Japan and Korea. Both trials aim to evaluate the safety and efficacy of the ultrasound RDN system in patients with uncontrolled hypertension.

Although there are positive results from SPYRAL HTN-OFF MED, RADIANCE SOLO, and SPYRAL HTN-ON MED trials, several limitations and unknown issues remain. Since RDN was performed in a small number of selected patients and follow-up was only up to 6 months, it is not clear whether the BP lowering effects can be sustained in the long-term. However, past trials have laid down lessons such that future trials are likely to be blinded, involve ambulatory blood pressure monitoring and have longer follow up periods.

CONCLUSION

There is progressively increasing evidence for RDN as an option for effective treatment in resistant hypertension. RDN could potentially reduce the morbidity and mortality risks associated with resistant hypertension in Malaysia.

CONFLICT OF INTEREST

None to declare.

CONSENT

Patients described in the above case reports have given written informed consent for the use of the data and publication of this article.

REFERENCES

1. SYMPLICITY HTN-1 Investigators. Catheter-based renal sympathetic denervation for resistant HTN: durability of blood pressure reduction out to 24 months. *Hypertension* 2011; 57: 911-7.
2. SYMPLICITY HTN-1 Investigators. Renal sympathetic denervation in patients with treatment-resistant HTN (the SYMPLICITY HTN-2 trial): a randomised controlled trial. *Lancet* 2010; 376: 1903-9.
3. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, et al. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med* 2014; 370: 1393-401.
4. Kandzari DE, Bohm M, Mahfoud F, Townsend RR, Weber MA, Pocock S, et al. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. *Lancet* 2018; 391: 2346-55.
5. Townsend RR, Mahfoud F, Kandzari DE, Kario K, Pocock S, Weber MA, et al. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRALHTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. *Lancet* 2017; 390:2160-70.
6. Kario K, Ogawa H, Okumura K, Okura T, Saito S, Ueno T, et al. SYMPLICITY HTN-Japan first randomized controlled trial of catheter-based renal denervation in Asian patients. *Circ J* 2015; 79: 1222-9.
7. Azizi M, Sapoval M, Gosse P, Monge M, Bobrie G, Delsart P, et al. Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multi-centre, open-label, randomised controlled trial. *Lancet* 2015; 385: 1957-65.
8. Mathiassen ON, Vase H, Bech JN, Christensen KL, Buus NH, Schroeder AP, et al. Renal denervation in treatment-resistant essential HTN. A randomized, SHAM-controlled, double-blinded 24-hr blood pressure-based trial. *J Hypertens* 2016; 34: 1639-47.
9. Azizi M, Schmieder RE, Mahfoud F, Weber MA, Daemen J, Davies J, et al. Endovascular ultrasound renal denervation to treat HTN (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. *Lancet* 2018; 391: 2335-45.
10. Mauri L, Kario K, Basile J, Daemen J, Davies J, Kirtane AJ, et al. A multinational clinical approach to assessing the effectiveness of catheter-based ultrasound renal denervation: The RADIANCE-HTN and REQUIRE clinical study designs. *Am Heart J* 2018; 198: 115-29.