Renal Denervation in the treatment of Resistant Hypertension

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ABSTRACT
Hypertension is a risk factor for coronary artery disease and stroke. Only about half of the patients with hypertension are adequately controlled on medical therapy, and about a quarter may develop severe or resistant hypertension. Resistant hypertension is defined as failure to achieve target blood pressure of <140/90 mmHg while on full doses of an appropriate three-drug regimen that includes a diuretic. Increasingly more attention has been paid to the potential of renal denervation (RDN) as treatment for resistant hypertension, guided by a better understanding of renal nerve anatomy.

RDN is undergoing transformation as a technology for the treatment of resistant hypertension. Early studies demonstrated efficacy in treating resistant hypertension patients with significant reduction in office blood pressure (BP). However, the randomised sham-controlled trial, Symplicity HTN-3, did not demonstrate any significant difference in BP reduction between the RDN and the sham control arm. Since then, further improvements have been made in developing second generation systems. Subsequent studies showed the importance of more distal and branch renal artery ablation, and multielectrode systems have been utilised. Two randomised sham-controlled trials, the SPYRAL HTN-OFF MED and SPYRAL HTN-ON MED studies showed the effectiveness of RDN with the second-generation radiofrequency ablation system. These studies showed that RDN significantly reduced office and 24-hour ambulatory BP when compared with sham control treatment. The RADIANCE-HTN SOLO trial also demonstrated efficacy using an ultrasound-based catheter system for RDN treatment of resistant hypertension. These trials have reinvigorated current clinical interest in RDN as treatment for resistant hypertension.

There is increasing evidence for RDN as an effective treatment for uncontrolled or resistant hypertension. The RDN procedure has also evolved with time, with an improved practice of delivering a larger number of ablations to distal vessels in addition to main renal arteries. The RDN procedure has a low complication rate and may provide an approach that could potentially reduce the morbidity and mortality risks associated with resistant hypertension in Malaysia.

KEYWORDS:
Renal Denervation, resistant hypertension

Hypertension is a risk factor for coronary artery disease and stroke.¹ The Malaysian National Health and Morbidity Survey in 2019 has shown that the prevalence of hypertension was 6.4 million, and 3 out of 10 people in Malaysia have hypertension.² Having increased levels of blood pressure (BP) increases the mortality risk³ and controlling hypertension reduces mortality related to ischaemic heart and cerebrovascular disease.⁴ It has been shown that even modest reductions in BP are associated with significant reductions in the rates of cardiovascular mortality.⁵ Only about half of the patients with hypertension are adequately controlled on medical therapy,⁶ and about a quarter may develop severe or resistant hypertension.⁷ Resistant hypertension is defined as failure to achieve target blood pressure of <140/90 mmHg while on full doses of an appropriate three-drug regimen that includes a diuretic. One study found that in Malaysia, resistant hypertension is present in nearly one in ten hypertensive patients on treatment.⁸

It is important to have a treatment option for patients with treatment resistant hypertension, who may subsequently develop end organ damage from hypertension. Over time, our understanding of the pathophysiology of hypertension has progressively improved. Studies of hypertension models have demonstrated that renal afferent and efferent sympathetic nerves have a significant role in the pathophysiology of hypertension.⁹ As a result, increasingly more attention has been paid to the potential of renal denervation (RDN) as treatment for resistant hypertension, guided by a better understanding of renal nerve anatomy.

Pathophysiology and Rationale for Renal Denervation
Over the years, there has been increasing evidence from studies that the sympathetic nervous system plays a significant role in the pathophysiology of hypertension.¹⁰ It has been shown that reduced activity of the renin-angiotensin system and reduced renal vascular resistance is involved in the antihypertensive effect of RDN in experimental rat models.¹¹ Furthermore, canine models demonstrated that renal nerve stimulation in both proximal and middle regions of the renal artery increased systolic BP by >10 mmHg.¹² RDN was therefore thought to be a method which can alter sympathetic activity, since surgical RDN has also previously been shown to reduce BP in several animal models of hypertension.¹³

The sympathetic nerves located around the renal arteries are derived from the celiac plexus, the lumbar splanchnic nerves,
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and the superior mesenteric ganglion. These nerves lie close to the renal artery, allowing the possibility of denervation through an endovascular approach. Previous studies showed that more nerve fibres are present in the proximal artery when compared to the distal segment. About half of the nerve fibres around the main artery are located within 2.5mm from the intima of the artery. In contrast, the nerves at the distal arteries are even closer to the lumen than those in the proximal segments, with a majority of the nerve fibres within 2mm from the intima. This knowledge has led to techniques to optimise the clinical outcome for renal denervation by targeting nerve fibres.

Renal sympathetic efferent nerves activate the renin-angiotensin-aldosterone system, hence leading to a decrease in office systolic BP of 26mmHg in the RDN group (n=364) compared to a decrease of 11.7mmHg in the control group (n=171) (Figure 2). 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. One possible reason for this could have been the lack of consistency in hypertensive medications taken, with medication changes occurring in 39% of patients over the period of the trial. Another proposed reason for these differences was variable operator experience in delivering RDN treatment.

Several other randomised controlled trials (RCT) have used RFA in renal denervation with variable results. The simplicity HTN-Japan trial was the first RCT of RDN in an Asian population involving RDN (n=22) and control (n=19) subjects. The 6-month office SBP change was -16.6±18.5mmHg for RDN subjects (p<0.001) and -7.9±21.0mmHg for control subjects (p=0.117). Another trial, the French DENER-HTN trial was an RCT involving patients with resistant hypertension. A group of patients on medications who were treated with RDN (n=48) was compared to a control group of patients treated with medication only (n=53). The mean change in daytime ambulatory systolic blood pressure at 6 months was -15.8mmHg (95% Confidence Interval, 95%CI: -19.7, -11.9) in the renal denervation group and -9.9mmHg (95%CI: -13.6, -6.2) in the group receiving antihypertensive medication. Another trial carried out in Denmark, the ReSet trial, is an RCT among patients with resistant hypertension. Sixty-nine patients with treatment-resistant hypertension were randomised to RDN (n=36) or a sham procedure (n=33). In this trial however, there were no significant differences when comparing RDN to a sham procedure at 6-month [+6.1±18.9 mmHg (RDN) vs. -4.3±15.1mmHg (SHAM)].

Developments in the Renal Denervation Technology

Since the publication of SYMPLICITY HTN-3 trial, further advances have been made in the technology for RDN. Studies have previously demonstrated that RF ablation was more effective when renal sympathetic nerves at the distal segment of the renal artery or the arterial branches are targeted. One study randomised patients with uncontrolled hypertension to RFA at the main renal artery (n=26) compared RFA at the distal branches of the renal arteries (n=25). At 6-month, the decrease in 24-hour ambulatory systolic BP (SBP) was greater in the distal branch treatment group compared to the main artery RFA group (22.6mmHg vs. 9.4mmHg; p<0.03). In another clinical study, there was better BP reduction at 3-month using the combined method compared to main vessel ablation only. With the previous Simplicity Flex ablation system (Medtronic, Minneapolis, MN, USA) it was challenging to achieve circumferential ablation. Therefore, more advanced systems have since been
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Fig. 1: Afferent and efferent renal sympathetic nerve targets for renal denervation.

Fig. 2: The Simplicity HTN-1 and HTN-2 trials showed significant drop when comparing RDN and controls, but Simplicity HTN-3 trial did not show a significant difference.

Fig. 3: Renal Denervation with the Spyral 4-electrode Catheter system.

developed with multi-electrode catheter design to increase the ease of use and reduce operator dependency. One such system, the Spyral catheter was designed as a 4-electrode system which delivers a maximum power of 6.5W for a duration of 60 seconds44 (Figure 3).

The SPYRAL HTN-OFF MED and SPYRAL HTN-ON MED, were designed as proof of concept studies for the Spyral catheter.37,38 These trials assessed BP response to RDN in patients with mild to moderate hypertension (office SBP of 150-180mmHg, 24-hr ambulatory SBP of 140-170mmHg). The SPYRAL HTN-ON MED trial assessed patients who were on 1 to 3 antihypertensive medications. Patients were randomised (1:1) to RDN or sham treatment in both trials. In these trials, the Spyral catheter allowed a more comprehensive RDN procedure that involved ablation in the distal main renal artery and arterial branches. Additionally, the operators had previous RDN experience, and a standardised approach was used to target all accessible renal arterial branches with a diameter of 3 to 8mm.

The SPYRAL HTN-OFF MED showed that at 3-month following RDN, there was significant reduction in both office and 24-hour ambulatory BP from baseline in the treatment group (-10/-5.3mmHg and -5.5/-4.8mmHg) 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-month (-9.0/-6.0mmHg for 24-hr ambulatory BP) (Figure 4). A rigorous procedural technique was adopted in this study, including more extensive ablutions involving the main vessel and the branches. The larger number of ablutions was not associated with an increase in adverse events.
Apart from RFA as described above, catheter-based ablation of renal nerves has also been shown to be effective using ultrasound. With this technology, ultrasound is emitted circumferentially via a piezoelectric crystal at the end of the catheter that is placed in the renal artery with the inflation of a water-cooled balloon (Paradise ultrasound system; ReCor Medical, Palo Alto, California). A multicentre, single-blind, sham-controlled trial (RADIANCE-HTN SOLO) studied catheter-based ultrasound in patients who were not on antihypertensive medications. The decrease in daytime ambulatory SBP (primary endpoint) from baseline to two months was greater in the RDN group (8.5mmHg, n=74) when compared to the sham group (2.2mmHg, n=72). The successful treatment using this method in the RADIANCE-HTN SOLO trial suggests that interruption of the renal nerves in any segment of the renal artery may be sufficient to achieve effective RDN.

Two additional RCTs with ultrasound-based ablation systems are ongoing. The RADIANCE-HTN TRIO trial is being conducted in the United States and Europe. The REQUIRE Systematic / Narrative Review Article

CONCLUSION

There is increasing evidence for RDN as an effective treatment for uncontrolled or resistant hypertension. The RDN procedure has also evolved with time, with an improved practice of delivering a larger number of ablations including distal vessels in addition to main renal arteries. The RDN procedure has a low complication rate. In the future, randomised controlled trials in larger populations with longer follow-up may further add to current evidence for the effectiveness of RDN treatment. RDN technology may provide an innovative approach that could potentially reduce the morbidity and mortality risks associated with resistant hypertension in Malaysia.

REFERENCES

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