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 <140/90mmHg 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.[1,2] 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.[3] Having increased levels of blood pressure (BP) increases the mortality risk[4] and controlling hypertension reduces mortality related to ischaemic heart and cerebrovascular disease.[5] It has been shown that even modest reductions in BP are associated with significant reductions in the rates of cardiovascular mortality.[6] Only about half of the patients with hypertension are adequately controlled on medical therapy,[7] and about a quarter may develop severe or resistant hypertension.[8] Resistant hypertension is defined as failure to achieve target blood pressure of<140/90mmHg 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.[9]

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.[10] 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.[11] 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.[12] Furthermore, canine models demonstrated that renal nerve stimulation in both proximal and middle regions of the renal artery increased systolic BP by >10mmHg.[13] 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.[14]

The sympathetic nerves located around the renal arteries are derived from the celiac plexus, the lumbar splanchnic nerves,

This article was accepted: 22 August 2021
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and the superior mesenteric ganglion.[15] 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.[16] 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.[17] This knowledge has led to techniques to optimise the clinical outcome for renal denervation by targeting nerve fibres.[18]

Renal sympathetic efferent nerves activate the renin-angiotensin-aldosterone system, hence leading to a decrease renal blood flow, as well as a decrease in urinary excretion of salt and water[19] (Figure 1). By decreasing efferent sympathetic nerve activity, RDN can lower BP. Additionally, sympathetic afferent activity also activates centrally, leading to further mediation of hypertensive response.[20] RDN can also reduce BP by decreasing centrally mediated renal afferent sympathetic nerve activity.[21] Both reductions of afferent and efferent renal nerve activity lead to a reduction in systemic vascular resistance which leads to the BP lowering effect.[22]

Renal Denervation Procedure in Early Clinical Trials

Since studies have shown that renal sympathetic nerves are located at a close distance to the renal arteries, radiofrequency ablation (RFA) via the intra-arterial route was first introduced to denervate sympathetic nerves in order to lower BP in patients with hypertension. The first-generation RFA system (Symplicity Flex; Medtronic, Minneapolis, Minnesota) is a catheter with single electrode. The system uses low power output (8W) to deliver RFA into the intraluminal surface of the renal artery via a single electrode catheter, with four to six ablations of 120 seconds each in the renal artery.[23] The early study (SIMPLICITY HTN-1 study) using this catheter was a proof of concept trial that included 45 patients who underwent RDN treatment.[24] Primary endpoints included safety and efficacy in lowering office BP. The patients had a mean baseline office BP of 177/101mmHg. The study demonstrated significant reduction in office systolic BP of 26mmHg in the RDN group compared to 12mmHg in the control group at six months (Figure 2).

Following this, a multicentre randomised controlled trial (SYMPLICITY HTN-2 study) studied patients with resistant hypertension with an office systolic BP of ≥160mmHg despite the prescription of ≥3 antihypertensive drugs, including a diuretic.[25] RDN was performed using the Simplicity Flex catheter and RDN treatment was compared to medical therapy in the study. The study found that the mean office BP at 6 months dropped by 32mmHg ($p<0.001$) in the RDN group (n=52) compared to BP drop of 12mmHg in the control group (n=54) (Figure 2). There was, however, some limitations for the first two Simplicity trials. Firstly, both studies were not blinded, and furthermore 24-hour ambulatory BP was not routinely tested. Hence, a further blinded randomised controlled trial, the Simplicity HTN-3 trial was conducted subsequently to overcome these limitations.

The Symplicity HTN-3 was a multicentre single blinded trial which randomised 535 patients to either RDN using Symplicity Flex or sham control (with 2:1 randomisation).[26] The trial compared an RDN group with a sham-controlled group of patients with an office systolic BP ≥160mmHg despite the prescription of ≥3 antihypertensive medications including a diuretic. The primary and secondary efficacy endpoints were the difference in office and 24-hour ambulatory BP reduction respectively between the two groups at 6-month. After six months following RDN treatment, there was a mean decrease in office systolic BP of 14.1mmHg 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.[27] Another proposed reason for these differences was variable operator experience in delivering RDN treatment.[28]

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.[29] 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.[30] 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).[31] 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.[32,33] 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).[34] 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.[35] 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

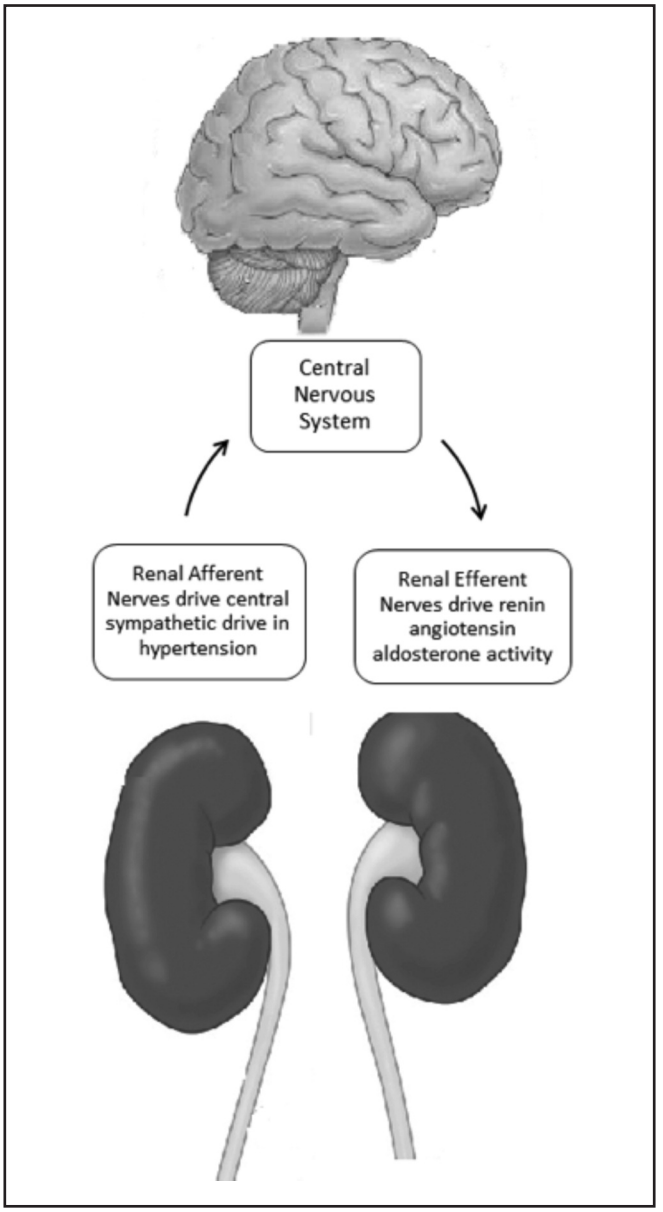

Fig. 1: Afferent and efferent renal sympathetic nerve targets for renal denervation.

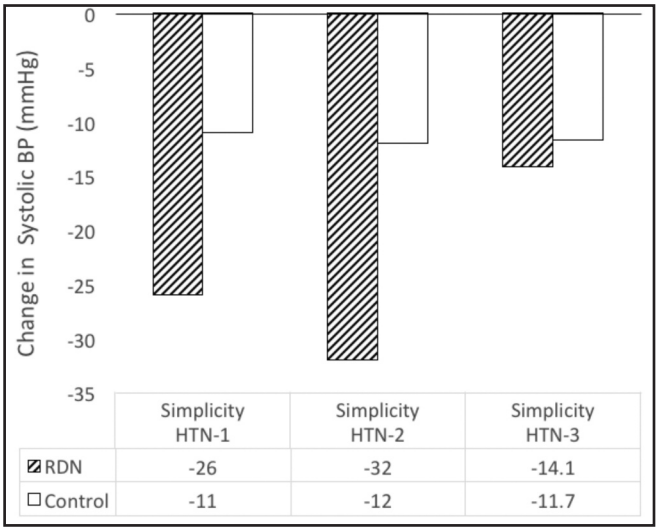

Fig. 2: The Simplicity HTN-1 and HTN-2 trials showed significant drop when comparing RDN and controls, but Simplicity HTN-3 trial did not show a significant difference.

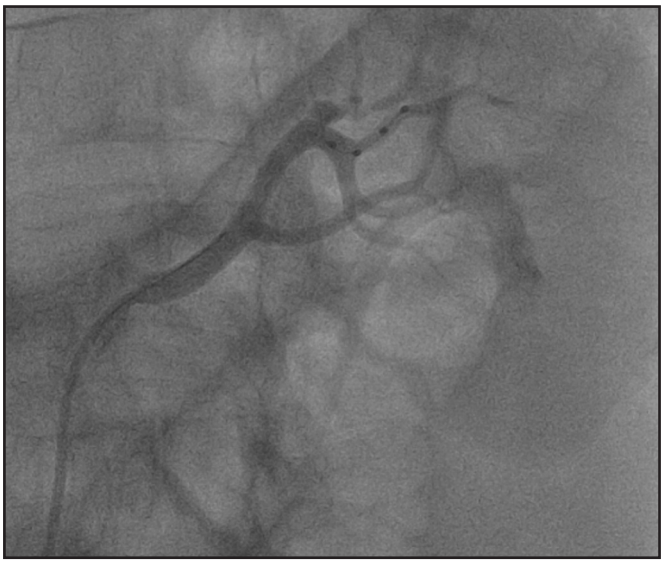

Fig. 3: Renal Denervation with the Spyral 4-electrode Catheter system.

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 seconds[36] (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 ablations involving the main vessel and the branches. The larger number of ablations was not associated with an increase in adverse events.

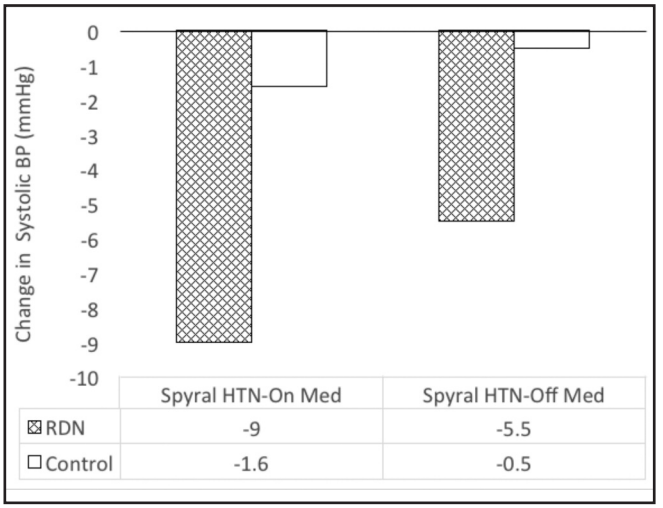

Fig. 4: Reduction of 24-hour Systolic BP in the Spyral HTN-On and HTN-Off Med trials.

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).[39] 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.[40] 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 (office BP >140/90mmHg despite treatment with three antihypertensive medications). The primary endpoint in both trials is the change in daytime ambulatory BP from baseline to six months.

Clinical Safety

Many studies have demonstrated a low complication and adverse event rate with RDN. Complications are commonly related to vascular access for example, haematoma and pseudoaneurysm at the femoral puncture site with an incidence of 1-2%.[41] Another complication is renal artery dissection with an incidence of <1%. There have also been reported cases of renal artery stenosis after the RDN procedure.[42] There has been no reports of significant deterioration of renal function after RDN.[43]

Potential Limitations of RDN trials

Although there are positive results from SPYRAL HTN-OFF MED, RADIANCE SOLO, and SPYRAL HTN-ON MED several limitations and unknown issues remain. Since RDN was performed in a small number of selected patients and follow-up was only up to six months in these studies, it is not clear whether the BP lowering effects can be sustained and also safety in the long-term is still not known. One other important factor is to determine whether RDN can reduce the number of antihypertensive drugs for long-term BP control, and this is currently not known.

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

1. Benjamin Ej, Blaha Mj, Chiuve Se, Cushman M, Das Sr, Deo R, et al. Heart disease and stroke statistics-2017 Update: A Report From the American Heart Association. Circulation 2017; 135(10): e146–603.
2. Solomonica A, Lavi S, Choudhury T, Bagur R. Renal denervation therapy beyond resistant hypertension. J Thorac Dis 2018; 10: 707-13.
3. National Institutes of Health (NIH) Ministry of Health Malaysia. National Health and Morbidity Survey 2019 Non-communicable diseases, healthcare demand, and health literacy. Published online: http://iptk.moh.gov.my/images/technical_report/2020/4_Infographic_Booklet_NHMS_2019_-_English.pdf Accessed 1 Aug 2021
4. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360: 1903-13.
5. Pezzini A, Grassi M, Lodigiani C, Patella R, Gandolfo C, Zini A, et al. Predictors of long-term recurrent vascular events after ischemic stroke at young age: the Italian Project on Stroke in Young Adults. Circulation 2014; 129: 1668-76.
6. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 2016; 387: 957–67.
7. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics–2012 update: a report from the American Heart Association. Circulation 2012; 125: e2–20.
8. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Circulation 2008;117: e510-26.
9. Chia YC, Ching SM. Prevalence and predictors of resistant hypertension in a primary care setting: a cross-sectional study. BMC Fam Pract 2014; 15: 131.

10. DiBona GF. Physiology in perspective: the wisdom of the body. Neural control of the kidney. Am J Regul Integr Comp Physiol 2005; 289: R633-41.
11. Grassi G, Mark A, Esler M. The sympathetic nervous system alterations in human hypertension. Circ Res 2015; 116: 976-90.
12. Foss JD, Fink GD, Osborn JW. Differential role of afferent and efferent renal nerves in the maintenance of early and late phase hypertension. Am J Physiol-Regul Integr Comp Physiol 2016; 310: R262-7.
13. Lu J, Wang Z, Zhou T, Chen S, Chen W, Du H, et al. Selective proximal renal denervation guided by autonomic responses evoked via high-frequency stimulation in a pre-clinical canine model. Circ Cardiovasc Interv 2015; 8: e001847.
14. Osborn JW, Foss JD. Renal nerves and long-term control of arterial pressure. Compr Physiol 2017; 7: 263-320.
15. DiBona GF, Kopp UC. Neural control of renal function. Physiol Rev 1997; 77: 75-197.
16. Tellez A, Rousselle S, Palmieri T, Rate Wr, Wicks J, Degrange A, et al. Renal artery nerve distribution and density in the porcine model: biologic implications for the development of radiofrequency ablation therapies. Transl Res 2013; 162: 381-9.
17. Sakakura K, Ladich E, Cheng Q, Otsuka F, Yahagi K, Fowler DR, et al. Anatomic assessment of sympathetic peri-arterial renal nerves in man. J Am Coll Cardiol 2014; 64: 635-43.
18. Mahfoud F, Tunev S, Ewen S, Cremers B, Ruwart J, Schulz-Jander D, et al. Impact of lesion placement on efficacy and safety of catheter-based radiofrequency renal denervation. J Am Coll Cardiol 2015; 66: 1766-75.
19. Osborn JW, Foss JD. Renal nerves and long-term control of arterial pressure. Compr Physiol 2017; 7: 263-320.
20. Kopp UC. Role of renal sensory nerves in physiological and pathophysiological conditions. Am J Physiol Regul Integr Comp Physiol 2015; 308: R79-95.
21. Hering D, Lambert EA, Marusic P, Walton AS, Krum H, Lambert GW, et al. Sub- stantial reduction in single sympathetic nerve firing after renal denervation in patients with resistant hypertension. Hypertension 2013;61: 457–64.
22. Ewen S, Cremers B, Meyer MR, Donazzan L, Kindermann I, Ukena C, et al. Blood pressure changes after catheter-based renal denervation are related to reductions in total peripheral resistance. J Hypertens 2015; 33: 2519-25.
23. Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet 2009; 373: 1275-81.
24. 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.
25. Symplicity HTN-2 Investigators, Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, et al. Renal sympathetic denervation in patients with treatment-resistant HTN (the SYMPLICITY HTN-2 trial): a randomised controlled trial. Lancet 2010; 376: 1903-9.
26. 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.
27. Kandzari DE, Bhatt DL, Brar S, Devireddy CM, Esler M, Fahy M, et al. Predictors of blood pressure response in the SYMPLICITY HTN-3 trial. Eur Heart J 2015; 36: 219-27.
28. Mahfoud F, Bakris G, Bhatt DL, Esler M, Ewen S, Fahy M, et al. Reduced blood pressure-lowering effect of catheter-based renal denervation in patients with isolated sys- tolic hypertension: data from SYMPLICITY HTN-3 and the Global SYMPLICITY registry. Eur Heart J 2017; 38: 93-100.
29. 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.
30. 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.
31. 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.
32. Henegar JR, Zhang Y, Hata C, Narciso I, Hall ME, Hall JE. Catheter-based radiofrequency renal denervation: location effects on renal norepinephrine. Am J Hypertens 2015; 28: 909-14.
33. Mahfoud F, Tunev S, Ewen S, Cremers B, Ruwart J, Schulz-Jander D, et al. Impact of lesion placement on efficacy and safety of catheter-based radiofrequency renal denervation. J Am Coll Cardiol 2015; 66: 1766-75.
34. Pekarskiy SE, Baev AE, Mordovin VF, Semke GV, Ripp TM, Falkovskaya AU, et al. Denervation of the distal renal arterial branches vs. conventional main renal artery treatment: a randomized controlled trial for treatment of resistant HTN. J Hypertens 2017; 35: 369-75.
35. Fengler K, Ewen S, Hollriegel R, Rommel KP, Kulenthiran S, Lauder L, et al. Blood pressure response to main renal artery and combined main renal artery plus branch renal denervation in patients with resistant hypertension. J Am Heart Assoc 2017; 6(8): e006196.
36. Whitbourn R, Harding SA, Walton A. Symplicity multi-electrode radio- frequency renal denervation system feasibility study. EuroIntervention 2015; 11: 104–9.
37. 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.
38. 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 (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. Lancet 2017; 390: 2160-70.
39. 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.
40. 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 de- signs. Am Heart J 2018; 198: 115–29.
41. Esler MD, Bohm M, Sievert H, Rump CL, Schmieder RE, Krum H, et al. Catheter-based renal denervation for treatment of patients with treat- ment-resistant hypertension: 36 month results from the SYMPLICITY HTN-2 randomized clinical trial. Eur Heart J 2014; 35: 1752–9.
42. Diego-Nieto A, Cruz-Gonzalez I, Martin-Moreiras J, Rama-Merchan JC, Rodriguez-Collado J, Sanchez-Fernandez PL. Severe renal artery stenosis after renal sympathetic denervation. JACC Cardiovasc Interv 2015; 8: e193-4.
43. Bohm M, Mahfoud F, Ukena C et al. First report of the Global SYMPLICITY Registry on the Effect of Renal Artery Denervation in Patients with uncontrolled hypertension. Hypertension 2015; 65(4): 766-74.