Int J Clin Exp Physiol. 2024;11(3):90-95.
https://www.ijcep.org

Review Article

Role of Interventional Physiology in Renal Denervation Therapy for Resistant Hypertension

Balaji Pishey Ashwathnarayan Rao[1,*], Smitha Ranoji Rao Varne[2]

[1]Associate professor of physiology, ESH Hypertension Specialist, Diabetologist, Sri Siddhartha Institute of Medical Sciences and Research Centre, T Begur, Bangalore, Karnataka, INDIA.
[2]Consultant Integrative Medicine and Nutritionist, Preksha Wellness and Yoga Center, Bangalore, Karnataka, INDIA.

ABSTRACT

Interventional physiology is a super specialty of physiology that involves procedures to study the physiological and technical aspects of blood flow, its velocity, Instantaneous wave-Free Ratio (iFR), pressure gradients in various organ systems like coronary, cerebral, renal, hepatic systems and recording and monitoring of various neurohormonal/neurophysiological signals, pressures during intraoperative and perioperative intervals and acts as an adjunct tool in differentiation between normal and abnormal events, responses and lesions. There have been significant advances in interventional cardiac (example: Evaluation using fractional flow reserve or non-hyperemic pressure ratios has become a gold standard for patients suffering from ischemic heart disease) and interventional neurophysiology [example: Intraoperative Neurophysiological Monitoring (IONM)], but there is strong need for increased enthusiasm and involvement of interventional physiologist in renal system as well. Renal Denervation (RDN) therapy for resistant hypertension is one of such fields and opportunity, where in pre-procedural work up and intra and post-procedural monitoring by interventional physiological techniques by a qualified interventional physiologist along with treating physicians can be game changer in a multidisciplinary team based therapeutical approach.

Keywords: Hypertension, Physiology, Renal denervation, Radiofrequency.

***Correspondence:**
Balaji Pishey Ashwathnarayan Rao
Associate Professor of Physiology, ESH Hypertension Specialist, Diabetologist, Sri Siddhartha Institute of Medical Sciences and Research Centre, T Begur, Bangalore, Karnataka, INDIA.
Email: drpaba@rediffmail.com, drpaba2@gmail.com

Received: 14-07-2024;
Revised: 06-09-2024;
Accepted: 22-09-2024.

INTRODUCTION

Hypertension is one of the leading causes of morbidity and mortality across the world and a strong cause for development of cardiovascular, cerebrovascular and chronic kidney diseases.[1,2]

Prevalence of hypertension has been exponentially increasing day by day and a recent epidemiological study ICMR- INDIAB, depicted that the overall occurrence of high blood pressure was 35.5% (95% CI 33.8-37.3; 35 172 of 111 439 individuals) in India.[3] Whereas, globally as per World Health Organization (WHO) 2023 report approximately 26% of the global population (972 million people) are suffering from high blood pressure and the occurrence is expected to increase to 29% or even higher by the year 2025. Even though resistant hypertension varies depending on the population and definition used, apparently 10 to 20% of patients with hypertension are non-responsive to medications in the presence of 3 or more antihypertensive agents of different categories, including a diuretic, at the highest and maximum tolerated dose. Sympathetic hyperactivity is one of the key etiological causes of resistant hypertension.[1,4,5]

With the advances in medical electronic technology, among the newer methods of treating hypertension, renal artery denervation has emerged as an adjuvant therapeutic option for patients with resistant hypertension. Renal Denervation (RDN) is a minimally invasive percutaneous procedure that can be performed by interventionist using a variety of methods, including i) Radiofrequency Ablation (RFA) in which a catheter is percutaneously used to position electrodes that generate thermal energy to damage the perivascular renal nerves. The multielectrode catheter parallelly delivers 60 sec of radiofrequency energy to four electrodes in contact with the renal vessel wall in spiral configuration. The design permits continuous blood flow during energy delivery, ensuring both vessel wall and electrode cooling during the RDN. The specific renal arteries with a diameter of 3-8 mM, including branches are targeted. ii) The ultrasound RDN system delivers ultrasound energy to thermally ablate the renal nerves. The catheter is positioned within the main renal arteries and centered by an integrated low-pressure, saline-filled cooling balloon to achieve a circumferential ring of ablation. Treatment is delivered sequentially to the distal, mid and proximal main renal arteries, with each treatment lasting

DOI: 10.5530/ijcep.2024.11.3.17

7 sec. iii) Alcohol-based RDN involves three retractable deep microneedles to deliver dehydrated alcohol into the perivascular space of the main and large accessory renal arteries (4-7 mM) causing nerve damage. iv) Chemical/neurotoxin injection in which Vincristine, an anti-neo-plastic agent with neurotoxic effect is injected into the perivascular space through the wall of the kidney artery. v) Selective renal infusion: 6-hydroxydopamine is selectively infused into the kidney to damage the noradrenergic nerve terminals.[1,6-8]

Renal arterial innervation

The kidney receives innervation from both afferent (sensory) and efferent (sympathetic) nerves, which form the renal plexus. The sympathetic afferent and efferent nerve fibers travel within the adventitial layer. The mean number of perivascular nerves appears more in the proximal and midsegments of the renal artery. There is also a reduction in the number of afferent fibers from proximal to distal segments and the density of innervation is lowest in the dorsal part of the artery.[1,9,10]

Afferent nerves

These nerves carry impulses from the kidney's sensory receptors to neuronal sites, including the subfornical organs, the hypothalamus and Nucleus Tractus Solitarius (NTS) in brainstem, which then modulates sympathetic outflow. They are mainly located in the pelvic region, the corticomedullary connective tissue and the major vessels.

Efferent nerves

These nerves control the kidney's vasculature, renin release and the excretion of urinary water and sodium. They are mainly located along the afferent and efferent arterioles near the glomerulus.

The renal plexus receives input from the celiac, aortico-renal plexuses and the least splanchnic nerves. The least splanchnic nerve is mainly responsible for afferent signaling from the renal system to the brain. The renal innervation is concentrated in several areas, including both the afferent and efferent arterioles of the glomerulus, macula densa, renal tubules and Juxtaglomerular Apparatus (JGA). The renal innervation works with the intrarenal Renin-Angiotensin Aldosterone System (RAAS) to control many aspects of the kidney's function, including Renal Blood Flow (RBF), Glomerular Filtration Rate (GFR), sodium and water reabsorption, angiotensin II secretion.[4,11]

Mechanism of reno- neurohormonal axis

The afferent sympathetic nerves emit signals from the renal system, particularly in response to kidney damage, to the hypothalamus, causing an increase in central sympathetic outflow resulting in increase in systemic blood pressure. The efferent sympathetic nerves start from the Central Nervous System (CNS) and then innervate the renal structures. Noradrenaline is the key neurohormone in reno- neurohormonal axis. Stimulation of sympathetic fibers causes vasoconstriction of both the afferent and efferent arterioles. However, afferent arteriole vasoconstriction is comparatively greater. This decreases RBF and GFR. The chief effects of efferent sympathetic nerves on the renal system are to enhance renin secretion, improve sodium reabsorption and cause renal vasoconstriction to decrease blood flow through renal arteries.[1,11]

The physiological mechanism of catheter-based RDN

The Physiological Rationale of RDN includes decrease in efferent sympathetic stimulation to kidneys and afferent renal signaling to the Central Nervous System (CNS), decrease in noradrenaline spillage, restoration of sodium excretion, enhancement in RBF and decrease plasma renin activity leading to reduction in blood pressure due to attenuation of vasoconstriction. Also, a lesser stimulation of the beta-adrenergic receptors of the JGA causes decreased renin secretion and reduced stimulation of Renin Angiotensin Aldosterone System (RAAS), thus attenuating increases in blood volume. Further, there is lesser stimulation to the alpha-adrenergic receptors, which is a dominant factor in vasoconstriction. Additionally, there is reduction in renal neprilysin activity, which ameliorates myocardial fibrosis and normalize left ventricular function in patients suffering from resistant hypertension with heart failure.[4,12,13]

Mostly commonly used method of RDN is radiofrequency ablation that thermally damages the perivascular tissue of the renal artery altering the efferent and afferent sympathetic nerves. Few decades ago, surgical sympathectomy was shown to offer remarkable benefits in the treatment of uncontrolled hypertension, however, this procedure was discontinued due to intolerable adverse effects such as postural hypotension and syncope episodes. RDN, however, is a more selective and sophisticated method compared to crude surgical sympathectomy and has strong scientific evidence. The beneficial effect of RDN is shown in Figure 1.

In a study involving 66 patients (mean±SD, 70.0±10.3 years; 76.3% men) who were involved in long-term follow up evaluations with a mean of 8.8±1.2 years post- RDN, found that the baseline, ambulatory systolic BP decreased by -12.1±21.6 (from 145.2 to 133.1) mmHg (p<0.0001) and diastolic BP by -8.8±12.8 (from 81.2 to 72.7) mmHg (p<0.0001). Average heart rate (HR/minute) remained unchanged. At long-term follow up, patients were on one less antihypertensive drug compared with baseline (p=0.0052). Estimated Glomerular Filtration (eGFR) rate was within the expected age-associated rate of decline from 71.1 to 61.2 mL/min per 1.73 m^2. And suggested that RDN results in significant reduction in both office and ambulatory systolic and diastolic BP at approximately 9-year of follow up after catheter-based RDN on lesser medications and without any serious complications.[14]

Another follow up study involving 39 patients who were involved in the 10-year Radio frequency RDN follow-up (average follow-up duration 9.4±0.7 years) having baseline office and 24-hr ambulatory systolic blood pressure were 164±23 mmHg and 153±16 mmHg, respectively, found that, after 10 years, the 24-hr ambulatory and office systolic blood pressure reduced by 16±17 mmHg ($p<0.001$) and 14±23 mmHg ($p=0.001$), respectively with the number of antihypertensive medications remaining unchanged from 4.9±1.4 to 4.5±1.2 drugs ($p=0.087$). The renal function assessed by eGFR rate decreased within the expected range from 69 (95% CI 63 to 74) to 60 mL/min/1.73m2 (95% CI 53 to 68; $p<0.001$). Continued pre-existing renal artery stenosis was recorded in two patients and one patient suffered from new onset of renal artery stenosis. And with no other complications during follow up period, they suggested that, renal denervation was safe and significantly reduced ambulatory and office blood pressure up to 10 years in patients with resistant hypertension.[15]

In a mammalian study involving 40 Spontaneously Hypertensive Rats (SHRs) which were categorized into four groups according to the injected quantities of phenol (10%): control group, 0.5 mL group, 1 mL group and 1.5 mL group, were subjected to RDN, demonstrated that denervation with 1 mL phenol (10% phenol in absolute ethanol) significantly and safely damaged renal sympathetic nerves and resulted in decrease in blood pressure among hypertensive mammals.[16]

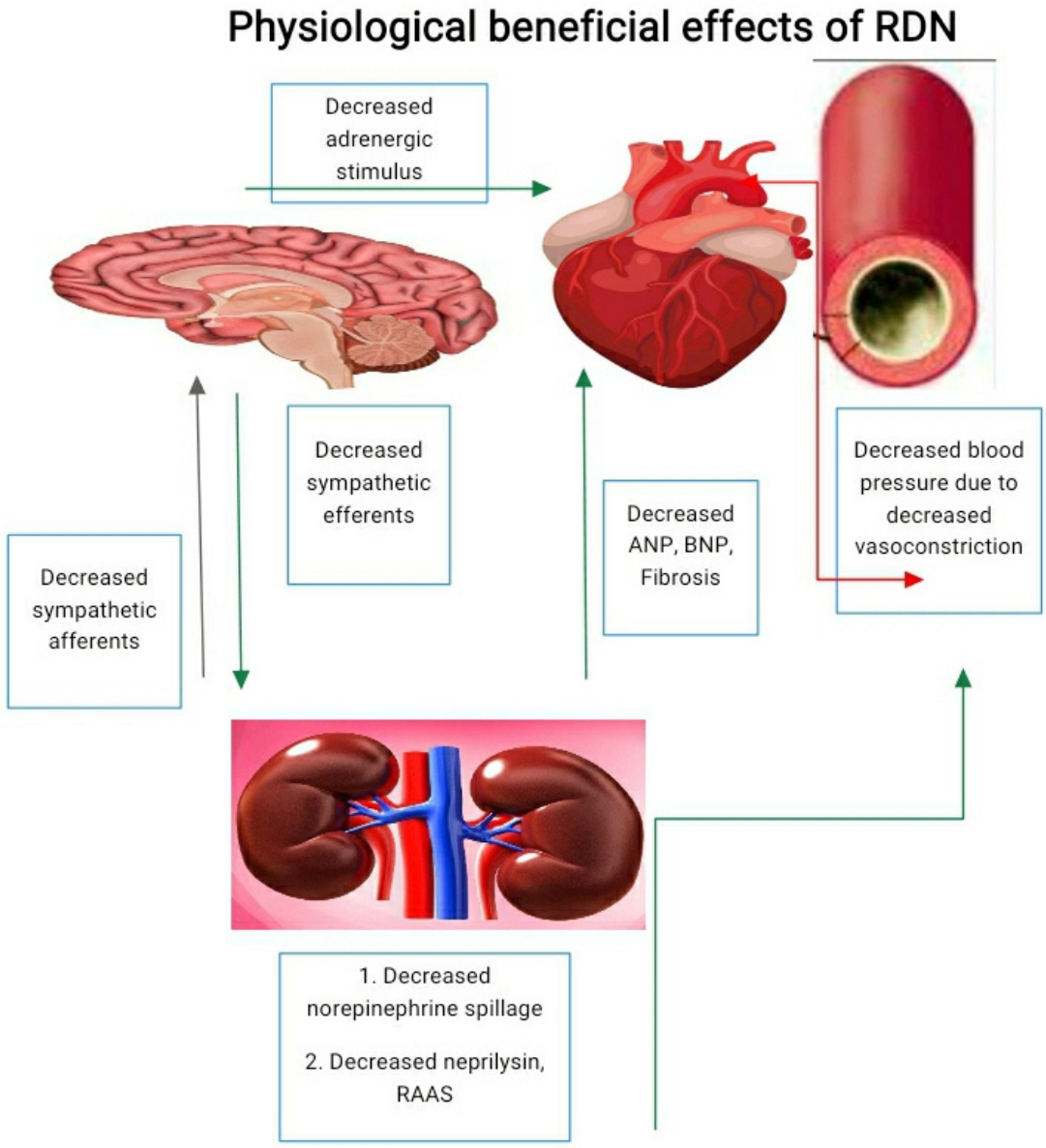

Figure 1: Shows beneficial effects of RDN. ANP: Atrial natriuretic peptide; BNP: Brain natriuretic peptide; RAAS: Renin angiotensin aldosterone system.

In a sham-controlled, randomized (2:1) clinical trial including 224 patients withdrawn from antihypertensive medications, subjected to ultrasound renal denervation demonstrated significant decrease in daytime ambulatory systolic blood pressure (baseline-adjusted between-group difference, -6.3 mmHg) as well as improvement for 6 of 7 secondary blood pressure outcomes compared with the sham procedure at 2 months without any serious complications.[17]

Similarly, many studies using radiofrequency and other forms of ablation/damage of renal nerves have shown a reduction in systemic blood pressure by lowering the Sympathetic Nervous System (SNS) tone.[18-21] There are some differences regarding the efficacy and complications of RDN, while using different methods (RFA/chemical/ultrasound/surgical) of RDN. Reduction of systemic vascular resistance remains the key reason for the antihypertensive effect of RDN. However, few studies have not shown much beneficial effects of Renal Denervation (RDN) for resistant hypertension.

The SYMPLICITY HTN-3 trial, which is a randomized, sham-controlled, blinded trial involving 535 patients, conducted across eighty-eight centers in the United States from October 2011 to May 2013, depicted that there was no difference between RDN and control (sham) groups regarding the change in office systolic blood pressure at 6 months: -14.13±23.93 mmHg (RDN group) vs -11.74±25.94 mmHg (sham-procedure) representing a between group change of -2.39 mmHg (p=0.26). Concordantly, no difference was demonstrated with respect to ambulatory systolic blood pressure (-6.75±15.11 mmHg vs -4.79±17.25 mmHg, p=0.98) between the RDN and control groups.[22]

In a meta-analysis of 9 RCTs involving 674 patients depicted the sham procedure (sham arm) for RDN depicted a significant decline in ambulatory systolic and diastolic blood pressure of -3.41 mmHg and - 2.44 mmHg, respectively as well as in declining Office Systolic and Diastolic Blood Pressure by -5.52 mmHg and - 2.13 mmHg, respectively, in patients with hypertension. And suggested that blood pressure itself might be sensitive to placebo-like effect and could challenge the blood pressure reducing efficacy of invasive interventions due to the sham effect.[23]

Another meta-analysis of fifteen Randomized Control Trials (RCTs) involving 857 patients subjected to RDN and 616 patients treated with medical therapy±sham procedure (control group), found no significant benefit of RDN on BP control in patients suffering from resistant hypertension compared to the control group.[24]

Limitations and drawbacks of RDN

The response in individuals to RDN is difficult to predict because of the differences in baseline sympathetic over activity or renal neurohormonal functions or in renal nerve ablation, approximately 10%-30% of patients do not respond to RDN.[25-29]

Bradycardia (slow heart rate), hypotension, pseudoaneurysm, renal artery stenosis, renal parenchymal damage with hematuria and contrast nephropathy, occurring in the post procedural phases.

Differences in anatomy of the renal artery/access site.

Health conditions that may enhance the risk of the procedure, such as a clotting or platelet disorders.

Severe kidney disease (eGFR <30 mL/min/1.73 m).

Ambiguity regarding predictors of success, which keeps physicians from using RDN in routine clinical practice.

Cost and need of well-equipped catheterization laboratories and experienced interventionist.

Till date, there is no clear established consensus regarding pre, intra-procedural and post procedural assessment and control of RDN success/failure. There is strong need to perform procedural work up (pre, intra and post) regarding the following basic clinical and physiological aspects:[10,30-38]

Patient selection regarding age, sex, etiology of resistant hypertension, stage of hypertension, status of sympathetic overactivity and adherence to pharmacological drugs and lifestyle modifications.

Thorough understanding and evaluation of renovascular physiology.

BP recording using ABPM (Ambulatory blood pressure monitoring) is paramount prior selection of patients for RDN procedure.

Thorough evaluation to rule out secondary hypertension.

Pre procedural study of gross and microscopic aspects and renal arterial imaging and the pattern of renal sympathetic fibers and renal tyrosine hydroxylase immunoreactivity.

Assessment of regenerative properties of the renal arterial innervation.

Pre procedural assessment of renal function particularly eGFR using serum creatinine or serum cystatin C.

Measurement of renal spillover of noradrenaline: Renal norepinephrine spillage rate is one of the accurate indicators of renal SNA and it is an invasive procedure that requires infusions of radiolabeled norepinephrine and venous sampling from centrally lines.

Measurement of plasma renin activity

Intraprocedural hemodynamic monitoring of intra-arterial blood pressure, renal blood flow and renal artery diameter.

Physiologic quantification of RDN by Renal Sympathetic Vasomotion (RSM), which is a novel method that provides intraprocedural feedback during RDN by measuring the cumulative occurrence of renal vasomotion that is vasoconstrictive and baroreflex-based.

Selecting the method (RFA/chemical/ultrasound/surgical) and marking of precise points of ablation/injection, irrespective of the variety of methods chosen for RDN, like distal ablation extending into branches of the main renal artery could produce more beneficial effects.

Interventionist to understand and have adequate hands-on training regarding RDN in animal models/simulations.

To get expertise with the particular instruments necessary for RDN and the procedural protocols to maximize the benefits and minimize harmful effects.

CONCLUSION

The role of interventional physiology is immense and invaluable in all the above-mentioned aspects and need to be embraced by interventionalists, so that, RDN could be executed with greater precision. Thus, not only effective blood pressure control can be achieved but also the risks of renal denervation, like renal artery occlusion, renal structural damage causing hematuria, renal vascular injury, access site infections, contrast induced kidney disease and post-procedure bradycardia and hypotension causing pre-syncope or syncope can by and large be prevented. We recommend further interventional physiological researches in future regarding evaluation and assessment of physiological phenomena in relation to renal denervation therapy, which would enhance the existing beneficial effects of RDN among patients having resistant hypertension. Thus, from an experimental set up to clinical bedside, RDN could become a valid therapeutic tool if used with caution to manage resistant hypertension.

ACKNOWLEDGEMENT

Nil.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ABPM: Ambulatory Blood Pressure Monitoring; **CNS:** Central Nervous System; **eGFR:** Estimated Glomerular Filtration Rate; **iFR:** Instantaneous Wave-Free Ratio; **IONM**: Intraoperative Neurophysiological Monitoring; **JGA:** Juxtaglomerular Apparatus; **RAAS:** Renin-Angiotensin-Aldosterone System; **RBN:** Renal Blood Flow; **RDN:** Renal Denervation; **RFA:** Radiofrequency Ablation; **RSM:** Renal Sympathetic Vasomotion; **SHR:** Spontaneously Hypertensive Rats; **SNS:** Sympathetic Nervous System; **SNA:** Sympathetic Nervous Activity; **WHO:** World Health Organization.

REFERENCES

1. Kario K, Okura A, Hoshide S, Mogi M. The WHO Global report 2023 on hypertension warning the emerging hypertension burden in globe and its treatment strategy. Hypertens Res. 2024;47(5):1099-102. doi: 10.1038/s41440-024-01622-w, PMID 38443614.
2. Balaji PA, Varne SR. Integrated review of management of hypertension by lifestyle changes, yoga, exercise, acupressure, herbal/plant and allopathic medications and newer interventions. Indian J Integr Med. 2023;5(1):1-9.
3. Anjana RM, Unnikrishnan R, Deepa M, Pradeepa R, Tandon N, Das AK, *et al.* ICMR-INDIAB collaborative study group. Metabolic noncommunicable disease health report of India: the ICMR-INDIAB national cross-sectional study (ICMR-INDIAB-17). Lancet Diabetes Endocrinol. 2023;11(7):474-89. doi: 10.1016/S2213-8587(23)00119-5 , PMID 37301218.
4. Heuser RR, Schlaich M, Sievert H. Renal denervation: A new approach to treatment of resistant hypertension. Springer; 2014.
5. Flack JM, Buhnerkempe MG, Moore KT. Resistant hypertension: disease burden and emerging treatment options. Curr Hypertens Rep. 2024;26(5):183-99. doi: 10.1007/s11906-023-01282-0, PMID 38363454.
6. Mahfoud F, Lüscher TF, Andersson B, Baumgartner I, Cifkova R, Dimario C, *et al.* Expert consensus document from the European Society of Cardiology on catheter-based renal denervation. Eur Heart J. 2013;34(28):2149-57. doi: 10.1093/eurheartj/eht154 , PMID 23620497.
7. Marcusohn E, Tobe SW, Dueck A, Madan M. Renal denervation for uncontrolled hypertension. CMAJ. 2023;195(43):E1475-80. doi: 10.1503/cmaj.230745, PMID 37931951.
8. Lauder L, Azizi M, Kirtane AJ, Böhm M, Mahfoud F. Device-based therapies for arterial hypertension. Nat Rev Cardiol. 2020;17(10):614-28. doi: 10.1038/s41569-020-0364-1 , PMID 32286512.
9. Tellez A, Rousselle S, Palmieri T, Rate WR 4th, 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(6):381-9. doi: 10.1016/j.trsl.2013.07.002, PMID 23911638.
10. Atherton DS, Deep NL, Mendelsohn FO. Micro-anatomy of the renal sympathetic nervous system: a human postmortem histologic study. Clin Anat. 2012;25(5):628-33. doi: 10.1002/ca.21280, PMID 21976355.
11. Pal GK, Pal P, Nivedita N. Comprehensive textbook of medical physiology. 1st ed Jaypee; 2017. p. 659-70.
12. Ram CV. Status of renal denervation therapy for hypertension. Circulation. 2019;139(5):601-3. doi: 10.1161/CIRCULATIONAHA.118.037937, PMID 30689414.
13. Thukkani AK, Bhatt DL. Renal denervation therapy for hypertension. Circulation. 2013;128(20):2251-4. doi: 10.1161/CIRCULATIONAHA.113.004660, PMID 24218440.
14. Sesa-Ashton G, Nolde JM, Muente I, Carnagarin R, Lee R, Macefield VG, *et al.* Catheter-based renal denervation: 9-year follow-up data on safety and blood pressure reduction in patients with resistant hypertension. Hypertension. 2023;80(4):811-9. doi: 10.1161/HYPERTENSIONAHA.122.20853, PMID 36762561.
15. Al Ghorani H, Kulenthiran S, Lauder L, Recktenwald MJ, Dederer J, Kunz M, *et al.* Ultra-long-term efficacy and safety of catheter-based renal denervation in resistant hypertension: 10-year follow-up outcomes. Clin Res Cardiol. 2024;113(10):1384-92. doi: 10.1007/s00392-024-02417-2, PMID 38451261.
16. Wang M, Han WZ, Zhang M, Fang WY, Zhai XR, Guan SF, *et al.* Chemical renal artery denervation with appropriate phenol in spontaneously hypertensive rats. J Geriatr Cardiol. 2018;15(11):695-702. doi: 10.11909/j.issn.1671-5411.2018.11.003, PMID 30534144.
17. Azizi M, Saxena M, Wang Y, Jenkins JS, Devireddy C, Rader F, *et al.* Endovascular ultrasound renal denervation to treat hypertension: the RADIANCE II randomized clinical trial. JAMA. 2023;329(8):651-61. doi: 10.1001/jama.2023.0713, PMID 36853250.
18. Kaiser L, Beister T, Wiese A, von Wedel J, Meincke F, Kreidel F, *et al.* Results of the ALSTER BP real-world registry on renal denervation employing the Symplicity system. EuroIntervention. 2014;10(1):157-65. doi: 10.4244/EIJV10I1A24, PMID 24472799.
19. Krum H, Schlaich MP, Sobotka PA, Böhm M, Mahfoud F, Rocha-Singh K, *et al.* Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. Lancet. 2014;383(9917):622-9. doi: 10.1016/S0140-6736(13)62192-3, PMID 24210779.
20. Esler MD, Krum H, Schlaich M, Schmieder RE, Böhm M, Sobotka PA, *et al.* Renal sympathetic denervation for treatment of drug-resistant hypertension: one-year results from the Symplicity HTN-2 randomized, controlled trial. Circulation. 2012;126(25):2976-82. doi: 10.1161/CIRCULATIONAHA.112.130880, PMID 23248063.
21. 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 randomized, sham-controlled, proof-of-concept trial. Lancet. 2017;390(10108):2160-70. doi: 10.1016/S0140-6736(17)32281-X, PMID 28859944.

22. Patel HC, Hayward C, Di Mario C, SYMPLICITY HT. SYMPLICITY HTN 3: The death knell for renal denervation in hypertension? Glob Cardiol Sci Pract. 2014;2014(1):94-8. doi: 10.5339/gcsp.2014.15, PMID 25054126.
23. Fernandes A, David C, Pinto FJ, Costa J, Ferreira JJ, Caldeira D. The effect of catheter-based sham renal denervation in hypertension: systematic review and meta-analysis. BMC Cardiovasc Disord. 2023;23(1):249. doi: 10.1186/s12872-023-03269-w, PMID 37173636.
24. de Jager RL, de Beus E, Beeftink MM, Sanders MF, Vonken EJ, Voskuil M, *et al.* Impact of medication adherence on the effect of renal denervation: the SYMPATHY trial. Hypertension. 2017;69(4):678-84. doi: 10.1161/HYPERTENSIONAHA.116.08818, PMID 28264922.
25. 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(4):219-27. doi: 10.1093/eurheartj/ehu441, PMID 25400162.
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(15):1393-401. doi: 10.1056/NEJMoa1402670, PMID 24678939.
27. Worthley SG, Tsioufis CP, Worthley MI, Sinhal A, Chew DP, Meredith IT, *et al.* Safety and efficacy of a multi-electrode renal sympathetic denervation system in resistant hypertension: the EnligHTN I trial. Eur Heart J. 2013;34(28):2132-40. doi: 10.1093/eurheartj/eht197, PMID 23782649.
28. Hutchinson BD, Keane D, Dodd JD. Renal sympathetic denervation: MDCT evaluation of the renal arteries. AJR Am J Roentgenol. 2013;201(2):W342-6. doi: 10.2214/AJR.12.8560, PMID 23883251.
29. Ji C, Walton J, Su Y, Tella M. Simultaneous determination of plasma epinephrine and norepinephrine using an integrated strategy of a fully automated protein precipitation technique, reductive ethylation labeling and UPLC-MS/MS. Anal Chim Acta. 2010;670(1-2):84-91. doi: 10.1016/j.aca.2010.04.051, PMID 20685421.
30. Bertog SC, Blessing E, Vaskelyte L, Hofmann I, Id D, Sievert H. Renal denervation: tips and tricks to perform a technically successful procedure. EuroIntervention. 2013;9 Suppl R:R83-8. doi: 10.4244/EIJV9SRA14, PMID 23732161.
31. Li S, Phillips JK. Patient selection for renal denervation in hypertensive patients: what makes a good candidate? Vasc Health Risk Manag. 2022;18:375-86. doi: 10.2147/VHRM.S270182, PMID 35592729.
32. Sakakura K, Ladich E, Edelman ER, Markham P, Stanley JR, Keating J *et al.* Methodological standardization for the pre-clinical evaluation of renal sympathetic denervation. JACC Cardiovasc Interv. 2014;7(10):1184-93. doi: 10.1016/j.jcin.2014.04.024, PMID 25240550.
33. Ukena C, Cremers B, Ewen S, Böhm M, Mahfoud F. Response and non-response to renal denervation: who is the ideal candidate? EuroIntervention. 2013;9 Suppl R:R54-7. doi: 10.4244/EIJV9SRA10, PMID 23732156.
34. Jain T, Kini A. Physiological assessment during interventional procedures. In: Kini A, Sharma SK, editors. Practical manual of interventional cardiology. Springer. Cham: Springer International Publishing; 2021. p. 51-60. doi: 10.1007/978-3-030-68538-6_4.
35. Nomura G, Kurosaki M, Takabatake T, Kibe Y, Takeuchi J. Reinnervation and renin release after unilateral renal denervation in the dog. J Appl Physiol. 1972;33(5):649-55. doi: 10.1152/jappl.1972.33.5.649, PMID 4635931.
36. Tsioufis C, Mahfoud F, Mancia G, Redon J, Damascelli B, Zeller T, *et al.* What the interventionalist should know about renal denervation in hypertensive patients: a position paper by the ESH WG on the interventional treatment of hypertension. EuroIntervention. 2014;9(9):1027-35. doi: 10.4244/EIJV9I9A175, PMID 24457275.
37. 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(7):635-43. doi: 10.1016/j.jacc.2014.03.059, PMID 25125292.
38. Pellegrino PR, Zucker IH, Chatzizisis YS, Wang HJ, Schiller AM. Quantification of renal sympathetic vasomotion as a novel end point for renal denervation. Hypertension. 2020;76(4):1247-55. doi: 10.1161/HYPERTENSIONAHA.120.15325, PMID 32829663.

Cite this article: Rao BPA, Varne SRR. Role of Interventional Physiology in Renal Denervation Therapy for Resistant Hypertension. Int J Clin Exp Physiol. 2024;11(3):90-5.