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Renal denervation and long-term results

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Arterial hypertension is a condition with a high prevalence in the global population and represents a major risk factor for adverse cardiovascular events, including stroke and death. Non-pharmacological and pharmacological interventions, with combination therapy as a standard strategy, are very effective in achieving optimal blood pressure (BP) goals. Nevertheless, in a non-negligible proportion of patients, drug therapy is ineffective at achieving BP targets or there is intolerance to specific anti-hypertensive medications. In this context, the use of invasive treatments for BP control, including renal denervation, represents a valuable therapeutic option. Renal denervation has experienced ups and downs over the years, with an initial growth period and a decline mainly linked to the initial negative results of a large, randomized trial. However, recent data from new trials and long-term follow-up of initial trials have confirmed the benefit and safety of the procedure by relaunching it in daily clinical practice. Additional research evaluating ablation methods other than radiofrequency are needed to be able to more clearly define the role of this procedure and the type of patients that can benefit most from it.

Introduction

Arterial hypertension, as is known, is a condition with a high prevalence in the general population. It is estimated that more than 9 million deaths worldwide can be attributed annually to the complications of arterial hypertension.[1]

Approximately 50% of patients become totally or partially non-adherent within a year to the prescribed anti-hypertensive medical treatment. This is particularly important given that even a modest decrease in blood pressure (BP) values can confer a substantial reduction in the risk of cardiovascular events.[2]

The reasons for non-adherence are numerous, but the two main causes are: (i) drug intolerance due to the development of adverse reactions and (ii) the patient's failure to take the prescribed therapy regularly. In addition to poor or non-adherence, resistant hypertension despite maximally tolerated anti-hypertensive therapy is present in ~10–20% of patients.[3]

This clinical background provides the rationale for using invasive anti-hypertensive treatment such as renal denervation (RDN) as a valid additive or alternative tool to conventional pharmacological therapies.

Rationale for the treatment of arterial hypertension with renal denervation

A strong body of evidence exists regarding the pathophysiological role of the sympathetic nervous system in arterial hypertension.

The activation of efferent fibres in the renal nerves leads to an increase in the activation of the renin-angiotensin-aldosterone system, with a consequent increase in plasma renin, sodium retention, and a reduction in renal perfusion. This, in turn, leads to an increase in the tone of the sympathetic afferent fibres, establishing a reciprocal strengthening circle between the central nervous system and the periphery with an increase in the central stimulus to arteriole vasoconstriction, heart rate, and myocardial contractility. All this results in an increase in the arterial BP.

Renal denervation may modulate or interrupt this downward spiral by targeting both afferent and efferent nerve fibres. Over the last few years, several histological studies have examined the effects and the pathological rationale of the effectiveness of RDN performed with the percutaneous technique first in porcine and then in human models. These studies have highlighted how both afferent and efferent fibres run circumferentially to the renal artery until they

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reach the organ parenchyma. On the other hand, the ganglia are located proximally at their origin from the aorta.

The main finding derived from the histological analyses is that the nerve fibres, despite being numerically lower, run closer to the arterial wall in the distal segment of the renal artery and in the proximal portion of its branches. Conversely, the distance between the arterial wall and the nerve fibres is highest in the proximal segment of the renal artery. As a consequence, the effects of energy delivered by RDN, particularly when radiofrequency (RF) is used, are more pronounced when impulses are delivered preferentially to the mid-distal tract of the renal artery. This is in line with a paradigm shift in clinical practice with the new generation ablation systems that are also able to reach the distal branches of the renal artery compared with the first-generation devices.

Of note, peri-arterial sympathetic fibres in the distal portion of the renal artery are more frequently post-ganglionic and therefore unmyelinated. The absence of Schwann cells, which provide the peri-axonal myelin, renders the fibres more susceptible to axonal damage induced by the ablation system. Furthermore, the lack of myelin determines a lower capacity for the regeneration of the nerve fibres, resulting in a greater long-term efficacy of the procedure.[4]

Effectiveness of first-generation radiofrequency ablation systems

The first RF ablation system (Symplicity Flex; Medtronic, Minneapolis, MN, USA) used a single, unipolar 4 Fr electrode catheter. The operator, rotating the catheter, manually performed multiple ablations at different points (typically 4–6 per renal artery) with a helical pattern in the mid-proximal segment of the vessel.

After the encouraging results of the first observational studies (e.g. SYMPLICITY HTN-1),[5] SYMPLICITY HTN-2 enrolled 106 patients with systolic BP (SBP) ≥ 160 mmHg (≥150 mmHg for diabetic patients) despite antihypertensive therapy with three or more drugs, including a diuretic, who were randomly assigned to RDN in addition to medical therapy vs. medical therapy alone (1:1 randomization). Although the primary endpoint [significant reduction in SBP and diastolic BP (DBP) at 6 months] was achieved, this trial had important limitations, mainly related to the small sample size and the lack of blinding.[6]

The subsequent SYMPLICITY HTN-3 trial was a randomized (2:1), single-blind, multi-centre study that enrolled 535 patients and included a sham procedure in the control arm (RDN vs. angiography of the renal arteries only). Although RDN proved safe with a few complications, mainly related to the vascular access site, the trial failed to show a significant difference in the primary endpoint of BP reduction at 6 months.[7]

Other randomized trials were designed to evaluate the efficacy of RF ablation, but of all, only three, including SYMPLICITY HTN-2, were able to demonstrate a significant difference (just a few mmHg) in patients undergoing renal ablation.[6]

The main studies on RDN and their principal results are presented in *Table 1*.

The results of these studies led to a progressive abandonment of the procedure until 2018, when the ESC guidelines for the management and treatment of arterial hypertension definitively contraindicated the procedure in daily clinical practice, reserving it only for cases included in clinical studies.[17]

The possible reasons for the failure of SYMPLICITY HTN-3 are many, but the main ones are the following:

- High proportion of patients with variation of medical therapy during the study period.[18]
- Operators involved, with little experience with the RF catheter for which only 6% of the treated patients had a circumferential ablation, as recommended by the protocol.[18]
- Use of a first-generation ablation system that made complete ablation less easy.[18]
- Identification of ablation points only in the main branch of the renal artery and not in the distal branches.[18]

The resurgence of renal denervation

Clinical and technical research on RDN devices was not withheld and subsequent trials showed that the ablation of the renal arteries in their distal branches resulted in an increased efficacy related to the new device iterations. In a study, patients randomized to RDN of the main renal artery and its branches vs. main renal artery achieved a significantly lower BP.[19]

Furthermore, since the publication of SYMPLICITY HTN-3, a second-generation RF ablation system has been developed, called the Symplicity Spyral (Medtronic), which unlike the first does not have a single electrode at the tip but has a flexible helical-shaped catheter tip that has four electrodes along its course that can ablate many different sites simultaneously, allowing for a more complete ablation (including the distal branches) and a less operator-dependent function.[20]

Two randomized, single-blind, multi-centre trials were designed using the Symplicity Spyral. In both cases, all operators had previous experience with renal ablation systems, and a well-defined standardized approach for the execution and indication of the ablation was indicated in the study protocol. In both, ambulatory BP monitoring (ABPM) was used as the endpoint, which allows for a more precise estimation of circadian variations in BP values. All patients were randomized 1:1 to RDN vs. renal angiography.

The first, SPYRAL HTN-OFF MED, included 331 hypertensive patients with SBP between 150 and 180 mmHg. To avoid influences related to pharmacological treatment adherence, all patients discontinued anti-hypertensive medications before randomization. The trial achieved all the pre-established efficacy endpoints, demonstrating a significant decrease in BP in the RDN group both with in-office measurement and with ABPM together with a significant reduction in the DBP.[12]

The recent SPYRAL HTN-ON MED trial enrolled 80 patients with SBP between 150 and 180 mmHg who had been stable for at least 6 weeks at the same dose of one to three anti-hypertensive drugs. Participants were randomly allocated to RDN vs. renal angiography. Again, the primary endpoint was met with a significant reduction in BP values in the 6-month RDN (ABPM) group. Furthermore, the trial also evaluated the efficacy of RDN

Table 1 Main studies involved in renal denervation

	Study and year	Catheter	Rand	Inclusion criteria	Pt enrolled	OnMed	FU	ΔSBP RDN-control (95% CI)
I-gen RF	SYMPLICITY HTN-1 (36M FU); 2013[8]	Symplicity Flex	N	SBP ≥160 mmHg and ≥3 medications	153 (88 pt at 36 m)	Y	36	−32.0 mmHg (−35.7 to −28.2)*
	SYMPLICITY HTN-2; 2010[6]	Symplicity Flex	Y	SBP ≥160 mmHg and ≥3 medications	106	Y	6	−8.0 mmHg (−17.9 to −0.9)
	SYMPLICITY HTN-3; 2014[7]	Symplicity Flex	Y	SBP ≥160 mmHg and ≥3 medications	535	Y	6	−1.96 mmHg (−5.0 to −1.1)
	SYMPLICITY HTN-3 (36M FU); 2022[9]	Symplicity Flex	Y	SBP ≥160 mmHg and ≥3 medications	282	Y	36	−22.1 mmHg (−27.2 to −17.0)
	DENER-HTN; 2015[10]	Symplicity Flex	Y	SBP ≥140 mmHg and/or DBP ≥80 mmHg and ≥3 medications	106	Y	6	−5.9 mmHg (−11.0 to −0.8)
	RDN in OSA; 2018	Symplicity Flex	Y	SBP ≥140 mmHg and ABPM ≥135 mmHg and ≥3 medications and moderate-to-moderate OSA	60	Y	3	−9 mmHg (−17 to −3)
	Pekarskiy *et al.*; 2017[11]	Symplicity Flex	Y	SBP ≥160 mmHg or DBP ≥100 mmHg and ≥3 medications	51	Y	6	−13.2 mmHg (−24.9 to −1.5)**
II-gen RF	SPYRAL HTN-OFF MED; 2020[12]	Symplicity Spyral	Y	SBP: 160-180 mmHg	331	N	3	−4.0 mmHg (−6.2 to −1.8)
	SPYRAL HTN-ON MED (36M FU); 2022[13]	Symplicity Spyral	Y	SBP: 150-180 mmHg and DBP: ≥90 mmHg and ABPM: 140-170 mmHg and ≥1-3 medications	80	Y	36	−10.0 mmHg (−16.6 to −3.3)
Ultrasound	RADIANCE-HTN SOLO; 2018[14]	Paradise	Y	BP: 140/90-180/110 mmHg and 0-2 medications or BP <140/90 mmHg and 1-2 medications	146	N	2	−6.3 mmHg (−9.4 to −3.1)
	RADIANCE-HTN TRIO; 2021[15]	Paradise	Y	BP ≥140/90 mmHg and ≥3 medications	136	Y	2	−4.5 mmHg (−8.5 to −0.3)
	REQUIRE; 2021	Paradise	Y	BP ≥150/90 mmHg and ABPM ≥140 mmHg and ≥3 medications	143	Y	3	−0.1 mmHg (−5.5 to −5.3)
US-RF	RADIOSOUND-HTN; 2018[16]	Symplicity Spyral and Paradise	Y	SBP ≥160 mmHg or DBP ≥910 mmHg and ≥3 medications	120	Y	3	−4.9 mmHg (−11.5 to 1.7)

at 36 months, identifying a statistically significant decrease in ABPM values in the experimental group.[13]

Recently, the 3-year results of the SYMPLICITY HTN-3 trial showed a significant reduction in in-office and outpatient BP in the experimental arm.[9]

These results (*Table 1*) have relaunched RDN as a useful additional therapeutic strategy in patients with arterial hypertension, demonstrating consistent efficacy. To date, therefore, RDN has returned to daily clinical practice, although large-scale observational studies are still needed to determine the efficacy of RDN in routine clinical practice.

Other renal denervation systems

In addition to the Symplicity catheter, other RF denervation systems have been developed, but the development was prematurely terminated after the first negative results of SYMPLICITY HTN-3, with the exception of the Vessix (Boston Scientific, Marlborough, MA, USA) and Iberis catheters (Terumo, Ann Arbor, MI, USA). However, clinical evidence is still scarce for these devices.

Furthermore, a denervation system has been developed that exploits the injection of ethanol into the periarterial adventitia through the arterial lumen using three needles emerging perpendicularly from the catheter. However, this system, despite the promising results of the first analyses, is still undergoing a more in-depth evaluation (ClinicalTrials.gov identifier: NCT03503773).

More consistent data are currently available for ultrasound denervation. The device (Paradise ultrasound system: ReCor Medical, Palo Alto, CA, USA) is based on a balloon catheter in the centre of which there is a piezoelectric crystal that, once inflated with water in the centre of the main renal artery, emits ultrasound circumferentially.

The RADIANCE-HTN SOLO trial included hypertensive patients who were not taking anti-hypertensive medications. Patients with BP $\geq$135/85 mmHg but <170/105 mmHg were randomly assigned to denervation by ultrasound or renal angiography only. The results favoured denervation with a greater and significant reduction in ABPM at 2 months compared with the control group.[14]

Two other trials were designed to confirm the results of RADIANCE-HTN SOLO: RADIANCE-HTN TRIO and REQUIRE. Both have a similar study design to the SOLO, with the exception that all enrolled patients were stabilized on a triple antihypertensive for at least 4 weeks before randomization. HTN TRIO enrolled patients from the USA and Europe, while REQUIRE enrolled Japanese and Chinese patients.

This difference in the two trials is important because of the following: while RADIANCE-HTN TRIO achieved the primary efficacy endpoint (a significant reduction of ABPM values at 2 months in the denervated group),[15] REQUIRE was ineffective in demonstrating its endpoint, and this, according to the authors, may be linked to the poor adherence to medical therapy of the enrolled patients and again to the strong climatic variations in temperature present in China and Japan that could have influenced the ABPM values. Long-term follow-up results for these patients are expected in the coming years.

Finally, a randomized trial (RADIOSOUND-HTN) compared the efficacy of RF ablation (using Symplicity Spyral) and ultrasound (using Paradise) including 120 patients with uncontrolled hypertension despite the use of three or more anti-hypertensive drugs with a 1:1:1 randomization (RF ablation of the main renal artery vs. RF ablation of the main renal artery and its branches vs. ultrasound ablation of the main renal artery). The results were encouraging, as the primary endpoint (reduction of ABPM at 3 months) was met for the ultrasound ablated vs. RF ablated group but only in the main renal artery, while the results were comparable between the ultrasound ablation and the RF ablation groups of the main renal artery and its branches.[16] This trial, however, has numerous limitations, the main ones certainly being the absence of a control group and the absence of tests for assessing adherence to drug therapy, which could have altered the BP values and therefore the results among the three groups. Further trials are therefore necessary to make a definitive and reliable comparison between the two methods.

Conclusions

Over the years, RDN has seen both light and shade, with an initial rapid growth, a subsequent decline mainly linked to the failure of SYMPLICITY HTN-3, and finally a renaissance with the expansion of the knowledge on this field. Recent new evidence on the long-term efficacy of the procedure has been added to the existing literature reinforcing the clinical and not only the experimental role of this type of treatment. However, further studies on larger populations are needed in order to better define the outcomes and the best profile of the patients who can benefit most from this technology. Meanwhile, the development of new devices that use methods other than RF such as ultrasound is expanding the spectrum of possibilities that operators and clinical cardiologists have in managing and treating patients suffering from arterial hypertension.

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Data availability

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References

1. Solomonica A, Lavi S, Choudhury T, Bagur R. Renal denervation therapy beyond resistant hypertension. *J Thorac Dis* 2018;**10**:707–713.
2. Ettehad D, Emdin CA, Kiran A *et al*. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016;**387**:957–967.
3. Noubiap JJ, Nansseu JR, Nyaga UF, Sime PS, Francis I, Bigna JJ. Global prevalence of resistant hypertension: a meta-analysis of data from 3.2 million patients. *Heart* 2019;**105**:98–105.
4. Sharp ASP, Tunev S, Schlaich M *et al*. Histological evidence supporting the durability of successful radiofrequency renal denervation in a normotensive porcine model. *J Hypertens* 2022;**40**:2068–2075.

5. Symplicity HTN-1 Investigators. Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. *Hypertension* 2011;**57**:911–917.
6. Symplicity HTN-2 Investigators. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. *Lancet* 2010;**376**:1903–1909.
7. Bhatt DL, Kandzari DE, O'Neill WW *et al*. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med* 2014;**370**:1393–1401.
8. Krum H, Schlaich MP, Sobotka PA *et al*. Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. *Lancet* 2014;**383**:622–629.
9. Bhatt DL, Vaduganathan M, Kandzari DE *et al*. Long-term outcomes after catheter-based renal artery denervation for resistant hypertension: final follow-up of the randomised SYMPLICITY HTN-3 trial. *Lancet* 2022;**400**:1405–1416.
10. Azizi M, Sapoval M, Gosse P *et al*. Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial. *Lancet* 2015;**385**:1957–1965.
11. 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 hypertension. *J Hypertens* 2017;**35**:369.
12. Böhm M, Kario K, Kandzari DE *et al*. Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pivotal): a multicentre, randomised, sham-controlled trial. *Lancet* 2020;**395**:1444–1451.
13. Mahfoud F, Kandzari DE, Kario K *et al*. Long-term efficacy and safety of renal denervation in the presence of antihypertensive drugs (SPYRAL HTN-ON MED): a randomised, sham-controlled trial. *Lancet* 2022;**399**:1401–1410.
14. Azizi M, Schmieder RE, Mahfoud F *et al*. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. *Lancet* 2018;**391**:2335–2345.
15. Azizi M, Sanghvi K, Saxena M *et al*. Ultrasound renal denervation for hypertension resistant to a triple medication pill (RADIANCE-HTN TRIO): a randomised, multicentre, single-blind, sham-controlled trial. *Lancet* 2021;**397**:2476–2486.
16. Fengler K, Rommel K-P, Blazek S *et al*. A three-arm randomized trial of different renal denervation devices and techniques in patients with resistant hypertension (RADIOSOUND-HTN). *Circulation* 2019;**139**:590–600.
17. Williams B, Mancia G, Spiering W *et al*. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J* 2018;**39**:3021–3104.
18. Kandzari DE, Bhatt DL, Brar S *et al*. Predictors of blood pressure response in the SYMPLICITY HTN-3 trial. *Eur Heart J* 2015;**36**:219–227.
19. Fengler K, Ewen S, Höllriegel R *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**:e006196.
20. Coates P, Tunev S, Trudel J, Hettrick DA. Time, temperature, power, and impedance considerations for radiofrequency catheter renal denervation. *Cardiovasc Revasc Med* 2022;**42**:171–177.