Review



Renal nerve ablation for resistant hypertension: facts, fictions and future directions

Davide Bolignano^{1,*} and Giuseppe Coppolino²

¹CNR - Institute of Clinical Physiology, c/o EUROLINE, Via Vallone Petrara 55-57, 89124 Reggio Calabria, Italy
²Renal Unit, Department of Health Sciences, "Magna Graecia" University, 88100 Catanzaro, Italy

*Correspondence: davide.bolignano@gmail.com (Davide Bolignano)

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Hypertension remains a major public health problem and one of the most relevant causes of cardiovascular mortality and morbidity worldwide. Roughly 10% of hypertensive individuals are considered as "resistant" as they are not able to achieve and maintain optimal blood pressure values despite the concurrent use of 3 antihypertensive agents of different classes at optimal doses. As resistant hypertension conveys a higher risk of adverse outcomes, the search for effective treatments to properly manage this condition has progressively surged as a true health priority. The renal nerve plexus plays a central role in regulating arterial blood pressure and renal sympathetic overactivity is a major component in the development and progression of hypertension. On these premises, minimally-invasive catheter based devices for renal nerve ablation have been developed and tested as an alternative treatment for resistant hypertension, but clinical study results have been ambiguous. This review provides a historical perspective on the scientific evidence forming the foundation of renal never ablation from accrued clinical evidence to possible future applications, reaching a tentative conclusion that more research and clinical experience is needed to fully reveal limits and potential indications of this procedure.

Keywords

Resistant hypertension; renal denervation; renal nerve ablation

1. Introduction

The prevalence of hypertension is constantly on the rise at the global level. Over one billion people are estimated to be affected by hypertension worldwide, and accounts for over ten million annual deaths due to cardiovascular complications (Benjamin et al., 2019; GBD 2017 Risk Factor Collaborators, 2018). Significant advancements have been made over the last two decades in prognostic and therapeutic research. Despite optimal drug and lifestyle prescriptions, the frequency of hypertensive individuals unable to achieve target blood pressure remains exceedingly high, spanning from 10% to 30% of the overall hypertensive population (Buhnerkempe et al., 2019).

Recent American guidelines (ACC/AHA) define hypertension as "resistant" when blood pressure values persist above target in spite of the concurrent use of 3 antihypertensive agents of different classes at optimal doses (Whelton et al., 2018). The exact causes behind resistant hypertension remain largely unknown although racial predisposition, age, poor medication compliance, and comorbidities such as obesity, sleep apnea, diabetes, and chronic kidney disease are potential co-determinants (Calhoun et al., 2008). The prognosis and clinical management of resistant hypertensive individuals remains problematic, and the search for alternative solutions to improve hard outcomes has rapidly surged as a health priority. Renal afferent and efferent sympathetic nerves are notoriously involved at the interface of blood pressure regulation (Larsen et al., 2014). The contribution of renal sympathetic overactivity to the development and progression of hypertension is a well-acknowledged concept (Fig. 1). This represents a plausible basis for renal denervation as a potential way to approach poorlymanageable cases of hypertension.

Since the late 1930s, radical splanchnic nerve and thoracic dorsal sympathectomy, complete interruption of the sympathetic renal plexus, was frequently employed to manage severe hypertension (Freyberg and Peet, 1937). Despite stable blood pressure lowering, this radical approach has predictably been abandoned after the advent of the pharmacological era due to the high rate of peri- and post-operative complications. The recent conception of advanced, minimally invasive catheter-based devices to selectively destroy the renal nerves (renal nerve ablation) has lifted new interest in exploring renal denervation as a possible approach for treating resistant hypertension.

In this manuscript, the most important technical options, clinical evidence and future perspectives of renal nerve ablation as a way to improve blood pressure in resistant hypertension.

2. Technique and devices for renal nerve ablation

2.1 Procedure and risks

Independently from the type of device and technique used (see Sections 2.2, 2.3 and 2.4), the procedure of renal nerve ablation usually starts with engagement of the femoral artery.

A full abdominal angiogram is performed to trace the route to renal arteries and to uncover potential obstacles or contraindications to renal denervation such as calcifications, plaques, or major anatomic variations. The first segment of renal vessels is engaged with a sheath or guide catheter, and the renal ablation device is



Figure 1. Contribution of the renal sympathetic system to the genesis of hypertension. Afferent fibers originating from the central nervous system targets the kidney at different tissue levels enhancing sodium and water retention, increasing renin release and decreasing renal blood flow which ultimately lead to an increased circulating volume. Efferent fibers arising from the renal pelvis conveys, in turn, sympatho-excitatory stimuli to autonomic regulatory nuclei in the midbrain leading to peripheral vasoconstriction and increased cardiac rate and output.

advanced up to the target treatment zone (Fig. 2). Strict contact between the ablation device and renal artery wall is ensured to maximize efficacy prior to balloon expansion, release of a selfexpanding shape memory polymer cage, or by the 3D-structure of some renal ablation devices that take on a helicoidal or spiral shape after removal of the guidewire.

For radiofrequency devices, vessel surface contact adequacy and ablative energy delivered are automatically estimated and regulated by complex software algorithms that rely on real time impedance tests. The treatment can be repeated in other accessory or distal segments of the same or contralateral renal arteries with sufficient diameter to accommodate the device. The procedure usually terminates with a final angiography to exclude structural damages like pseudoaneurysms, dissections, or thrombi.

When performed by an expert operator, renal nerve ablation is usually considered as a relatively safe procedure. Nevertheless, apart from periprocedural pain and potential contrast reactions, various adverse events or sequelae directly related to the technique have been described. These may include femoral artery pseudoaneurysm, renal artery dissection, vasospasm, transient dizziness, bradycardia, hypotensive episodes, pitting oedema, and anaemia. Although the vast majority of these events had very low or nooccurrence during large randomized controlled trials, the risk of such complications was not statistically significant as compared with controls. In this regard, two independent meta-analyses confirmed that renal denervation did not convey a higher risk of femoral artery pseudo-aneurysm, hypotensive or hypertensive episodes and long-term hyperkalaemia (Pappaccogli et al., 2018; Coppolino et al., 2017). Conversely, both meta-analyses evidenced a significantly increased risk of bradycardia episodes.

2.2 Radiofrequency devices

High energy delivered by radiofrequency application has been the first and most studied technique for renal nerve ablation. The Symplicity System (Medtronic, Minnesota, US) is a curved catheter coupled with a unipolar electrode that increases tissue temperature up to 40-75 °C by delivering 8 W radiofrequency energy. Radiofrequency ablation is performed in the distal ramifications of the renal artery and then repeated in the proximal branches after device retraction. The Symplicity Spyral (Medtronic, Minnesota, US) is the evolved spiral version of the Symplicity catheter. In this device, four radiofrequency electrodes are placed on a shape memory polymer to cover the four quadrants of the renal artery and branch vessels. This spiral design allows a circumferential treatment which avoids energy concentration into a single point maximizing efficacy and reducing number and time of applications.



Figure 2. Overview on the procedural technique of renal nerve ablation. After engagement of the femoral artery, the catheter-based device is advanced from aorta until the first segment of renal vessels and, from there, up to the established treatment zone. After ablative treatment ends (whatever the type) the procedure can be repeated in distal segments of the same renal artery with sufficient diameter to accommodate the device or in the contralateral renal artery.

Other similar radiofrequency devices with a helicoidal structure include the EnligHTN system (Abbott, Illinois, US), which consists of a multi-electrode basket that delivers ablative energy to four defined sites, and the Thermocool (Biosense-Webster, California, US), which is a multi-electrode, saline-irrigated catheter. The Vessix System (Boston Scientific, Massachussets, US) is another radiofrequency catheter coupled with a low-pressure balloon and irrigation ports for electrode cooling. Another helical, balloon-coupled catheter, the OneShot system (Medtronic, Minnesota, US), is currently off the market. Other radiofrequency catheters include the SyMapCath (Terumo Corporation, Japan), the Golden leaf catheter (Shanghai Golden Leaf MedTec Co., China), the PRDS-001 System (Otsuka, Japan), and the Synaptic device (Synaptic Medical Limited, China). Unlike all these devices that reach the renal artery via a traditional femoral access, the Iberis Renal Sympathetic Denervation System (Terumo Corporation, Japan) represents only steerable device specifically designed for radial access.

2.3 Ultrasound-based devices

Alternative to radiofrequency, renal ablation can be achieved by high energy generated by focused ultrasound application. However, this technique has been recently conceived so that fewer devices are available to date. The TIVUS (Cardiosonic, Israel), the Sound 360 system (Sound Interventions, New York, US), the firstgeneration Kona (Kona Medical, Washington, US) and the Paradise (ReCor Medical, California, US) systems are device-based catheters coupled with a piezoelectric micro-transducer placed inside a low-pressure balloon that delivers ultrasound energy over a 30-seconds application in a circumferential manner. Recently, an advanced non-invasive version of the KONA system has been designed to deliver ultrasound energy externally, thus avoiding invasive vascular catheterization. Unfortunately, a sham-controlled trial testing the efficacy of this device has been stopped at interim analysis due to futility (Neuzil et al., 2016).

2.4 Other techniques for renal nerve ablation

Beyond energy-mediated destruction, selective renal nerve ablation can be obtained by targeted administration of neurotoxic agents. For instance, a balloon-sheathed device with microneedles (Bullfrog Micro-Infusion Device, Mercator MedSystems, California, US) has been used to inoculate vincristine into the media of renal arteries with successful sympathetic renal neurolysis (Stefanadis et al., 2013a,b,c); however, reliable data on the effects on blood pressure control with this therapy are still lacking. Similar to vincristine, other neurolytic agents such as the neurotropic agent NW2013 are currently being investigated (Kipshidze et al., 2017).

Selective nerve disruption may also be achieved by perivascular injection of alcohol in a relatively safe manner (Fischell et al., 2016). In this regard, ethanol inoculation by the Peregrine catheter (Ablative Solutions, Michigan, US), a triple micro-needle catheter-based system, is currently being studied in two large ongoing randomized, sham-controlled trials. Cryoablation of renal nerves by a standard cardiac catheter (Freezor(R)Xtra, Medtronic, Minnesota, US) significantly improved blood pressure control in a small series of three patients with resistant hypertension who did not respond to radiofrequency (Prochnau et al., 2013). Similar positive findings on the efficacy of cryotherapy were reported by a following larger uncontrolled study (Prochnau et al., 2014), setting the stage for upcoming, multicenter randomized trials. Finally, vascular brachytherapy may be used to ablate renal sympathetic nerves through β -radiation exposure that trigger nerve apoptosis and tissue fibrosis (Waksman et al., 2013). A dedicated device, the Novoste (Best Vascular Inc., Virginia, US) catheter, has recently been conceived for such purpose and will be object of intensive investigation.

Table 1 summarizes the main existing techniques/devices for renal nerve ablation and the current level of evidence from clinical studies.

3. Clinical trials of renal nerve ablation: from hope- to fail- to resurgence

The efficacy and safety of renal nerve ablation in resistant hypertension has been investigated by a plethora of uncontrolled studies (Krum et al., 2014; Fischell et al., 2016; Tsioufis et al., 2015; Verheye et al., 2015; Sievert et al., 2017; Prochnau et al., 2013, 2014) that have laid the ground for more elaborate and randomized controlled trials (Table 2).

The vast majority of RCTs used the radiofrequency catheter Symplicity, driven from enthusiastic results from a single, proofof-concept, uncontrolled study (Krum et al., 2014) supported by Medtronic. Findings obtained from recent studies have pooled meta-analyses of randomized evidence (Pappaccogli et al., 2018; Coppolino et al., 2017), which provide negative or uncertain conclusions about the true usefulness of renal nerve ablation that improve blood pressure control in resistant hypertension.

In a large multicenter, prospective, open-label trial; the SYM-PLICITY HTN-2 (Symplicity et al., 2010) study had106 patients with resistant hypertension that were randomized to renal denervation or standard medical therapy. At 6 months, outpatient systolic/diastolic blood pressure decreased in the dominant arm by

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Device name (manufacturer)	Technique of renal nerve ablation	Highest level of evidence available
Symplicity System (Medtronic, Minnesota, US)	Radiofrequency-generated energy delivered from a catheter-based device placed into the renal artery	Multicenter, randomized, sham-controlled tri- als completed
Symplicity Spyral (Medtronic, Minnesota, US)	As above but device designed with a spiral shape	Multicenter, randomized, sham-controlled tri- als completed
OneShot system (Medtronic, Minnesota, US; formerly Covidien)	As above	-Small open-label uncontrolled study com- pleted
		-Device currently off-market
EnligHTN system (Abbott, Illinois, US;	As above	-Two non-randomized studies completed
formerly St. Jude)		-Large randomized, open-label trial ongoing
Vessix System (Boston Scientific,	As above	-Non randomized study completed
Massachussets, US)		-Larger sham-controlled randomized trial ongo- ing
Thermocool (Biosense-Webster, California, US)	As above but saline-irrigated	Small RCT (sham controlled) completed
PRDS-001 System (Otsuka, Japan)	As above	Large sham-controlled RCT ongoing
SyMapCath (Terumo Corporation, Japan)	As above	Large sham-controlled RCT ongoing
Synaptic device (Synaptic Medical Limited, China)	As above	Large sham-controlled RCT ongoing
Golden leaf catheter (Shanghai Golden Leaf MedTec Co., China)	As above	Large sham-controlled RCT ongoing
Iberis Renal Sympathetic Denervation System (Terumo Corporation, Japan)	As above but specifically designed for radial access	Large sham-controlled RCT ongoing
Paradise system (ReCor Medical, California, US)	As above but energy is ultrasound-generated	-Large randomized, double-blind, sham- controlled, study ongoing
TIVUS (Cardiosonic, Israel)	As above but energy is ultrasound-generated	-Open-label uncontrolled study completed- Randomized, double-blind, sham-controlled, cohort study ongoing
Kona Surround Sound (Kona Medical, Washington, US)	As above but energy is ultrasound-generated. In the second generation version, ultrasound is de- livered externally	-Small open-label uncontrolled study completed-Sham-controlled randomized trial of second-generation device stopped at interim analysis due to futility
Sound 360 system (Sound Interventions, New York, US)	As above but energy is ultrasound-generated	Very limited experience
Freezor(R)Xtra (Medtronic, Minnesota, US)	As above but energy is derived from cryother- apy	-Small proof-of-concept studies completed- Pilot, non-randomized, open-label controlled study on-going
Bullfrog Micro-Infusion Device (Mercator MedSystems, California, US)	Neurolysis induced by vincristine	-Pre-clinical evidence available-Pilot, non- randomized, open-label controlled study on-going
Peregrine catheter (Ablative Solutions, Michi- gan, US)	Nerve disruption by perivascular injection of ethanol	-Pre-clinical evidence available-Multicenter, randomized, sham-controlled trials ongoing

32/12 mmHg (p < 0.0001) with no changes among controls and a between-group difference of 33/11 mmHg (p < 0.0001). Similar positive findings were reported by the DENERHTN study (Azizi et al., 2015) in which 106 resistant hypertensive individuals were randomized to renal denervation plus a standardized stepped-care

antihypertensive treatment versus medical therapy alone. Systolic ABPM decreased at 6 months by 15.8 mmHg in the dominant arm versus 9.9 mmHg in the control arm with a baseline-adjusted difference of -5.9 mmHg (95% CI -11.3 to -0.5; p = 0.03). In contrast with these positive results, the PRAGUE-15 study (Rosa et

al., 2015) failed to demonstrate a clear superiority of renal nerve ablation when compared to an intensified antihypertensive drug regimen including the addition of spironolactone. In fact after 6 months, a significant reduction in 24-hour- and outpatient- average systolic blood pressure was observed in both the renal denervation and the control group with no significant difference in the between-group. Similarly, another small RCT of renal nerve ablation versus intensive medical drug treatment, the OSLO RDN study (Fadl Elmula et al., 2014) has prematurely been stopped for futility as outpatient systolic and diastolic blood pressure remained unchanged in the dominant group while reduced among controls.

The SYMPLICITY HTN-3 (Bhatt et al., 2014), another large (535 participants), multicenter randomized study, was designed with a sham-controlled approach with outcome-assessors blinding in order to minimize possible detection and performance bias. Unexpectedly, the mean systolic blood pressure decreased at 6 months in both the renal denervation $(-14.13 \pm 23.93 \text{ mmHg})$ and the sham-control group (-11.74 \pm 25.94 mmHg) with a nonsignificant difference in the between-group (p = 0.26). Similar negative results were reported also for 24-h ambulatory blood pressure monitoring (ABPM) (Bakris et al., 2014). Failure of the SYM-PLICITY HTN-3 was echoed by two other single-center shamcontrolled, randomized studies, the RESET (Mathiassen et al., 2016) and the Symplicity Flex (Desch et al., 2015), which evidenced the lack of superiority of renal denervation over control in improving systolic ABPM and in reducing the number of needed antihypertensive medications.

The unexpected failure of the SYMPLICITY HTN-3 and the other sham-controlled trials has raised a debate over the possible reasons beyond this surprising halt.

In this regard, adequate patient selection could have played a crucial role. Large registry evidence suggests that individuals with isolated systolic hypertension or wide pulse pressure are less likely to respond to renal denervation as a consequence of arterial stiffness and a deranged vasopressor response to sympathetic control (Mahfoud et al., 2017). In addition, subgroup analyses of the SYMPLICITY HTN-3 participants stratified by racial origin indicate that Caucasian patients are more prone to benefit from the procedure in terms of systolic BP reduction (Kotsis and Stabouli, 2014) while differences in BMI seem to be non-influential (Bhatt et al., 2014). Therapeutic compliance could be another key-point. Targeted investigation of the SYMPLICITY HTN-3 in this regard underlined that roughly 40% of subjects underwent known therapeutic changes during the trial plus an additional high rate of drug non-adherence that would otherwise not have been known to the investigators (Patel et al., 2016).

The uncertain success of renal nerve ablation itself has been pointed out as another aspect to be taken into account. An improvement in blood pressure, the main clinical indicator of efficacy of the procedure, may require up to one month to be clinically apparent. This is mostly due to the fact that functional nerve impairment, as obtained by radiofrequency energy, is preceded by tissue inflammation, degeneration, and fibrosis that require a welldefined time to manifest. Partial or unsuccessful renal nerve ablation may also depend from structural limits of the device. In such respect, more technically advanced catheters have been studied with a helicoidal or spiral design that allow energy to be delivered in a circumferential manner instead of a focused single renal artery spot. In addition to this, denervation performed in the distal vessel branches of renal vessels may improve ablation success as the juxtaposition distance between renal nerves and the artery lumen increases as the nerves track proximally in the direction of the vessel origin. The SYMPLICITY HTN-3 study underestimated the high operator dependence of results in terms of the interpretation and repeatability of the procedure. Roughly one-third of operators who participated in this study had no former or limited experience with renal nerve ablation, and the majority of them performed only one or two procedures in the trial (Bhatt et al., 2014).

Results from the two multicenter trials specifically designed to overcome many possible reasons of failure of the SYMPLIC-ITY HTN-3 and have recently given new hope for the future of renal denervation. The SPYRAL HTN-OFF and ON MED trials (Townsend et al., 2017; Kandzari et al., 2018) were two randomized, sham-controlled studies of renal nerve ablation by the lastgeneration Symplicity Spyral catheter in the absence (SPYRAL HTN-OFF MED) and presence (SPYRAL HTN-ON MED) of antihypertensive treatment. A 3-month analyses of the SPYRAL HTN-OFF MED (Townsend et al., 2017) showed little significant reduction in blood pressure among individuals undergoing renal denervation as compared with sham (5.0 and 4.4 mmHg in 24h systolic and diastolic ABPM and 7.7 and 4.9 mmHg in office blood pressure, respectively). Similarly, clinically limited benefits were confirmed by a more recent 6-month interim data analysis of the SPYRAL HTN-ON MED (Kandzari et al., 2018), in which the differences in systolic and diastolic drop between the renal denervation and the sham-control group (7.4 and 4.1 mmHg for 24h-ABPM and 6.8 and 3.5 mmHg for office blood pressure, respectively).

4. Future scenarios of clinical application of renal nerve ablation

Solid evidence has accumulated indicating that a deranged renal sympathetic activity could be detrimental in a series of other pathological conditions including renal disease, arrhythmias, obstructive sleep apnea, and metabolic syndrome (Linz et al., 2018). Future therapeutic targets of renal nerve ablation could move beyond the treatment of resistant hypertension. For instance, a recent systematic review and meta-analysis collecting data from 52 studies (2898 participants) has demonstrated that renal function is not significantly reduced up to at least 9 months after the renal nerve ablation, while in some cases it may improve even more (Sanders et al., 2017). In this view, renal nerve ablation could be studied as an additive renoprotective tool in a well-defined subset of individuals with pathologically high blood pressure. The rationale for such an application would be corroborated by previous reports showing a positive impact of renal denervation on GFR and proteinuria in experimental models of renal failure (Lubanda et al., 2017).

In patients with persistent atrial fibrillation, renal nerve ablation prevents or even ameliorates atrial remodeling (Schirmer et al., 2015; McLellan et al., 2015) and improves rate control (Kiuchi et al., 2017; Qiu et al., 2016) independently from blood pressure lowering.

In addition, renal denervation was able to reduce ventricular

ectopic activity and ICD shocks in individuals with dilated cardiomyopathy and electrical storm, as evidenced by a pooled analysis of 13 cases from five large international centers (Ukena et al., 2016).

			Table 2. Efficacy data	a from main randomiz	ed controlled trials c	on renal nerve ablation in resist	tant hypertension
Study ID	Year	Design	Population characteristics	Intervention	Comparator	Outcomes	Results
Symplicity HTN-2 (Symplicity et al., 2010)	2010	Multicenter, randomized, open-label	Individuals with uncon- trolled hypertension aged 18-85, systolic BP ≥ 160 (≥ 150 in diabetes) and ≥ 3 anti-hypertensive drugs	Renal nerve ablation (n = 53) by the Sym- plicity radiofrequency catheter plus standard treatment	Standard treatment alone (n = 54)	-Office blood pressure values	Blood pressure in the renal denervation group reduced by 32/12 mmHg (SD 23/11, baseline of 178/96 mmHg, $p < 0.0001$) but did not differ from baseline in the control group. Between-group differences in blood pressure at 6 months were 33/11 mmHg ($p < 0.0001$). At 6 months, 41 (84%) of 49 patients who underwent renal denervation had a reduction in systolic blood pressure of 10 mmHg or more, compared with 18 (35%) of 51 controls ($p < 0.0001$)
DENERHTN (Azizi et al., 2015)	2014	Multicenter, randomized, open-label	Individuals with uncon- trolled hypertension aged $18-75$, BP $\geq 140/90$ and \geq 3 anti-hypertensive drugs including diuretic	Renal nerve ablation ($n = 53$) by the Sym- plicity radiofrequency catheter plus a stan- dardized stepped-care antihypertensive treat- ment	Standardized stepped-care antihy- pertensive treatment alone (n = 53)	-Daytime systolic ABPM	Decrease of -15.8 mmHg (95% CI -19.7 to -11.9) in the renal dener- vation group versus -9.9 mmHg (95% CI -13.6 to -6.2) in the control group, with a baseline-adjusted difference of -5.9 mmHg (95% CI -11.3 to -0.5; <i>p</i> = 0.03)
PRAGUE-15 (Rosa et al., 2015)	2014	Multicenter, randomized, open-label	Individuals with uncon- trolled hypertension aged ≥ 18, systolic BP > 140 and ≥ 3 anti-hypertensive drugs including diuretic	Renal nerve ablation (n = 52) by the Sym- plicity radiofrequency catheter	Intensified treat- ment including spironolactone (n = 54)	-24h systolic ABPM -Office systolic blood pres- sure	0.001 in renal denervation versus -8.1 [95% CI -12.7, -3.4] mmHg; p = 0.001 in control group -Office Systolic BP decrease of -12.4 [95% CI: -17.0, -7.8] mmHg; p < 0.001 in renal denervation versus -14.3 [95% CI: -19.7, -8.9] mmHg; $p < 0.001$ in control group -No significant differences between groups
OSLO RDN (Fadl Elmula et al., 2014)	2014	Single- center, randomized, open-label	Individuals with uncon- trolled hypertension aged 18-80, systolic BP > 140 and ≥ 3 anti-hypertensive drugs including diuretic	Renal nerve ablation (n = 9) by the Sym- plicity radiofrequency catheter	Adjusted drug treat- ment (n = 10)	-Office blood pressure values	Systolic and diastolic BP changed from 160 \pm 14/88 \pm 13 to 132 \pm 10/77 \pm 8 mmHg at 6 months ($p < 0.0005$ and $p = 0.02$ respectively) in the control group with no significant change in the active group. Study was prematurely stopped for futility
Symplicity HTN-3 (Bhatt et al., 2014; Bakris et al., 2014)	2015	Multicenter, randomized, patients and outcome assessors- blinded	Individuals with uncon- trolled hypertension aged $18-80$, systolic BP ≥ 160 and ≥ 3 anti-hypertensive drugs including diuretic	Renal nerve ablation (n = 364) by the Sym- plicity radiofrequency catheter plus standard treatment	Sham procedure plus standard treat- ment (n = 171)	-Office systolic blood pressure -Mean 24h ABPM -Safety end point: composite of death, end-stage renal disease, embolic events resulting in end- organ damage, renovascular co- mplications, or hypertensive cr- isis at 1 month or new renal- artery stenosis of nore than 70% at 6 months	-Mean (+/-SD) change in systolic blood pressure at 6 months was -14.13+/-23.93 in the denervation group vs11.74+/-25.94 mmHg in the sham-procedure group ($p < 0.001$ for both comparisons of the change from baseline; $p = 0.26$ between-group difference). -Change in 24h ABMP systolic blood pressure was -6.75+/-15.11 in the denervation group vs4.79+/-17.25 mmHg in the sham-procedure group ($p = 0.98$ between-group difference).

	Results	-Similar reductions in daytime systolic ABPM compared with baseline at 3 months [-6.2 +/- 18.8 mmHg (RDN) vs6.0 +/- 13.5 mmHg (SH- AM)] and at 6 months [-6.1 +/- 18.9 mmHg (RDN) vs4.3 +/- 15.1 mm Hg (SHAM)]. Hg (SHAM)]. -Mean usage of antihypertensive medication (daily defined doses) at 3 months was equal [6.8 +/- 2.7 (RDN) vs. 7.0 +/- 2.5 (SHAM)]	Mean change in 24h systolic ABPM in the intention to treat cohort at 6 months was -7.0 mmHg (95% CI -10.8 to -3.2) for patients undergoing denervation and -3.5 mmHg (95% CI -6.7 to -0.2) in the sham group ($p = 0.15$)	Change in blood pressure was significantly greater at 6 months in the renal denervation group than the sham-control group for office systolic blood pressure (difference -7.7 mmHg; $p = 0.025$), 24h systolic ABPM (difference -5.0 mmHg; $p = 0.0051$), office diastolic blood pressure (difference -4.9 mmHg; $p = 0.0478$), and 24h diastolic ABPM (difference -4.4 mmHg; $p = 0.0292$)	Change in blood pressure was significantly greater at 6 months in the renal denervation group than the sham-control group for office systolic blood pressure (difference -6.8 mmHg; $p = 0.0205$), 24h systolic ABPM (difference -7.4 mmHg; $p = 0.0651$), office diastolic blood pressure (difference -3.5 mmHg; $p = 0.0478$), and 24h diastolic ABPM (difference -4.1 mmHg; $p = 0.0292$)
	Outcomes	-Daytime systolic ABPM -Mean usage of anti-hyp- ertensive medications	-24h systolic ABPM	-Office blood pressure -24h ABPM	-Office blood pressure -24h ABPM
Table 2. Continued	Comparator	Sham procedure (n = 33)	Sham procedure (n = 36) plus drug treatment	Sham procedure (n = 42)	Sham procedure (n = 42) : standard deviation
	Intervention	Renal nerve ablation (n = 36) by the Symplicity ra- diofrequency catheter	Renal nerve ablation (n = 35) by the Symplicity ra- diofrequency catheter plus drug treatment	Renal nerve ablation (n = 38) by the Symplic- ity Spyral radiofrequency catheter	Renal nerve ablation (n = 38) by the Symplic- ity Spyral radiofrequency catheter RDN: renal denervation, SD
	Population characteristics	Individuals with uncon- trolled hypertension and daytime systolic ABPM \geq 45 mmHg follow- ing 1 month of stable medication	Individuals with un- controlled hypertension aged $18-75$ and ≥ 3 anti-hypertensive drugs including diuretic	Individuals with mild uncontrolled hypertension aged 20-80, office systolic BP = $150 - 180$ and dias- tolic ≥ 90 and $24h$ -systolic ABPM = $140 - 170$	Individuals with mild uncontrolled hypertension aged 20-80, office systolic BP = 150 - 180 and dias- tolic ≥ 90 and 24h-systolic ABPM = 140 - 170 initoring, BP: blood pressure, 1
	Design	Single- center, randomized, single- blinded	Single- center, randomized, single- blinded	Multicenter, randomized, patients and outcome assessors- blinded	Multicenter, randomized, patients and outcome assessors- blinded ood pressure mo
	Year	2015	2015	2017	2018 Ilatory bl
	Study ID	RESET (Mathiassen et al., 2016)	Symplicity- FLEX (Desch et al., 2015)	SPYRAL HTN- OFF MED (Townsend et al., 2017)	SPYRAL HTN- ON MED (Kandzari et al., 2018) ABPM: ambu

5. Conclusions

The enthusiastic results of the first uncontrolled pilot studies and the open label SYMPLICITY HTN-2 trial were unexpectedly contradicted by negative findings from the SYMPLICITY HTN-3 and other sham-controlled trials that bring renal denervation to a grinding halt.

However, the identification of possible factors explaining such failure and the recent "bitter-sweet" results from the SPYRAL HTN-OFF/ON MED studies in terms of clinical effectiveness have kept the door ajar. Two main lines of research are currently on the horizon. The first mostly relies on a large bunch of shamcontrolled, multicenter studies aiming at testing large populations the efficacy, safety, and potential clinical applicability of approaches for renal denervation not employing radiofrequency devices (e.g. ultrasound, brachytherapy, cryotherapy or ethanol injection).

The second, parallel line is to keep working on more advanced, last-generation radiofrequency catheters to be tested in clinical studies designed to overcome pitfalls of previous trials, such as the appropriate selection of participants, procedure optimization, and the adequate management of anti-hypertensive drug regimen.

In any case, renal nerve ablation still remains a very promising technique for treating resistant hypertension; however, additional research efforts to clarify limits, potential, and indications should be considered.

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Conflict of Interest

The authors state that there are no conflicts of interest to disclose.

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