REVIEW ARTICLES

Novel approaches to the treatment of patients with resistant hypertension: renal sympathetic denervation

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Abstract

Background: Hypertension continues to be a major burden of public health concern despite the recent advances and proven benefit of pharmacological therapy. A certain subset of patients has hypertension resistant to maximal medical therapy and appropriate lifestyle measures. Resistant hypertension continues to pose a major challenge to clinicians worldwide and has serious implications for patients who are at increased risk of cardiovascular morbidity and mortality with this diagnosis. Pharmacological therapy for resistant hypertension follows guidelines-based regimens, although there is surprisingly scant evidence for beneficial outcomes using additional drug treatment after three antihypertensives have failed to achieve target blood pressure. Through modulation of renin secretion, glomerular filtration rate and renal absorption of sodium, the sympathetic innervation of the kidneys plays an important role in the pathogenesis of hypertension. A novel catheter-based technique for renal sympathetic denervation (RSDN) as a new therapeutic avenue has great promise for the treatment of resistant hypertension. Renal denervation has the unique advantage of offering the denervation at the renal level, thus mitigating the systemic side effects. Various trials evaluated the role of renal denervation in the management of resistant hypertension and have found promising results. More studies are underway to evaluate the role of renal denervation in patients presenting with resistant hypertension in different scenarios.

Conclusions: This review included the physiology of the renal sympathetic nervous system and the renal nerve anatomy. Furthermore, the RSDN procedure, technology systems, and RSDN clinical trials as well as findings besides antihypertensive effects were discussed. Findings on safety and efficacy seem to suggest that renal sympathetic denervation could be of therapeutic benefit in refractory hypertensive patients. Despite the fast pace of development in RSDN therapies, only initial and very limited clinical data are available. Large gaps in knowledge concerning the long-term effects and consequences of RSDN still exist, and solid, randomized data are warranted.

Key words: renal sympathetic denervation, resistant hypertension.

Introduction

Arterial hypertension epidemiology and control

The prevalence of hypertension is high and is growing steadily. In 2000, about 1 out of 4 adults (>20 years) were affected worldwide, and its prevalence is expected to increase to 1 out of 3 adults, reaching 1.56 billion in 2025 [1]. Hypertension is an independent major risk factor of cardiovascular events as stroke, heart attack, heart failure and kidney failure, being responsible for 62% of cerebrovascular diseases and 49% of ischemic heart disease [2]. Each increase in systolic blood pressure by 20 mmHg and diastolic blood pressure by 10 mmHg doubles the rate of cardiovascular mortality in 10 years [3].

The American Heart Association [4] and the Joint National Committee [5] define resistant hypertension as persistently high blood pressure (systolic and diastolic blood pressure>140 and 90 mmHg, respectively) despite medication administered, which includes three antihypertensives of different classes in appropriately tolerated maximum doses, one of which is a diuretic. It is necessary to cautiously differentiate resistant hypertension from uncontrolled hypertension caused by sub-optimal pharmacological treatment, non-compliance to treatment and secondary hypertension. The prevalence of resistant hypertension is often underestimated for various reasons, including inadequate sample size and exclusion of patients with resistant hypertension from large clinical trials [6, 7]. Kaplan et al estimated that up to 5% of patients in general clinics and about 50% of patients in clinics for kidney diseases suffer from resistant hypertension [6].

Renal sympathetic nervous system and hypertension

Maintenance of normal blood pressure readings is due to the coordinated action of several systems, the sympathetic nervous system playing an important role among them. The increase in sympathetic activity correlates with all hypertension phenotypes, central sympathetic activity, measured at the level of muscular sympathetic activity, being increased in all grades of hypertension compared to normotensive patients [8].

The important role of the renal sympathetic nervous system (SNS) in hypertension initiation and maintenance has been demonstrated through animal experiments and human experience, either by measuring its activity in hypertensive subjects or by monitoring the changes in blood pressure readings after sympathetic manipulations [9,10].

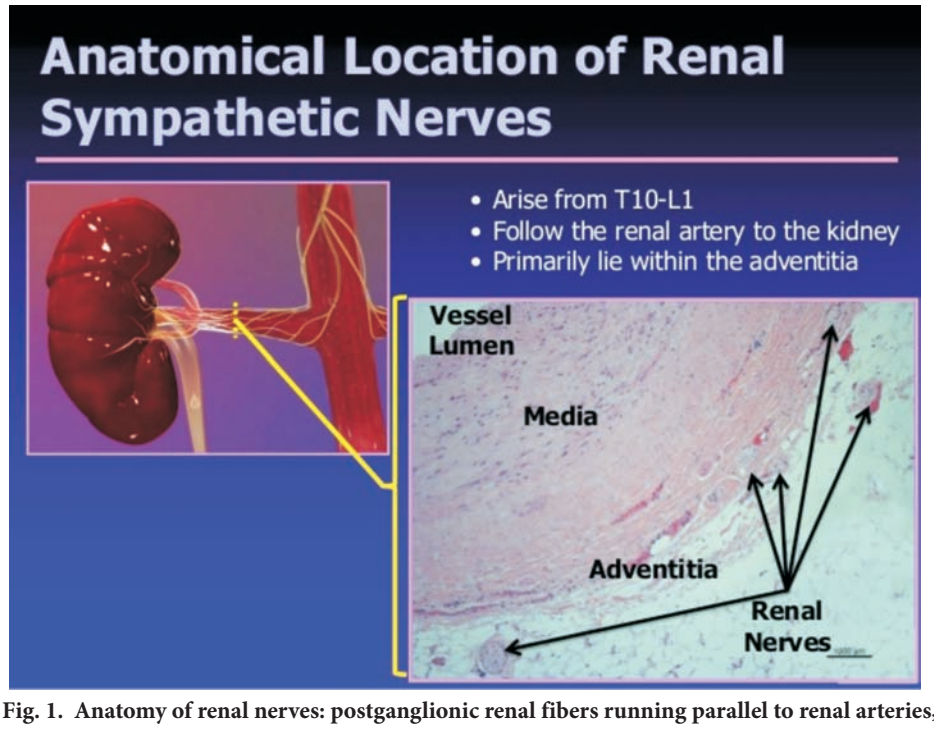


Fig. 1. Anatomy of renal nerves: postganglionic renal fibers running parallel to renal arteries, primarily situated around the adventitia.

The renal sympathetic nervous system is composed of efferent fibers directed from the central nervous system (CNS) to kidneys and afferent fibers having an opposite direction. The preganglionic axons of neurons, that originate in the T10-L2, interact with postganglionic renal nerves at the level of sympathetic pre- and paravertebral ganglia. Postganglionic renal fibers run parallel to the renal arteries, located around the adventitia and enter through the renal hilum to innervate renal tubules, blood vessels and the juxtaglomerular apparatus [11] (fig. 1).

By increasing the production of norepinephrine, these efferent fibers transmit stimuli from the CNS to kidneys and contribute to volumetric homeostasis and blood pressure values, facilitating tubular reabsorption of sodium, followed by hydrosaline retention, and renin secretion, further stimulating the renin-angiotensin-aldosterone system, renal vasoconstriction with the subsequent reduction of the renal blood flow [11, 12, 13, 14]. Oppositely, the kidneys transmit neural responses to the CNS through afferent fibers, also located around the adventitia of renal arteries [15, 16, 17].

Afferent renal sympathetic fibers have an extensive network in the renal pelvis and transmit signals from two types of receptors: mechanical-sensitive receptors that respond to increase in hydrostatic pressure and chemosensitive receptors that are activated by hypoxia and renal ischemia. The signals from these receptors pass through ipsilateral dorsal ganglia to the CNS, especially to the paraventricular nucleus of the hypothalamus [16, 18]. This stimulation of the afferent nervous system leads to increase in blood pressure readings through release of vasopressin, and increase in the systemic vascular resistance. In addition, afferent fibers communicate with the contralateral kidney, thus balancing the unilateral impairment of hydrosaline excretion, underlying the reno-renal reflux [19].

Previous experience of lumbar sympathectomy in the treatment of hypertension

Recognition of the important role that the sympathetic nervous system plays in the pathogenesis of hypertension has led to the development of a surgical approach, known as radical lumbar-dorsal splanchectomy, which interrupts the release of catecholamines [20]. This technique, developed by Smithwick in 1938, reduced blood pressure readings and mortality, but led to severe unacceptable side effects [20, 21]. Several uncontrolled clinical trials on surgical sympathectomy have shown a significant decrease in blood pressure, reduction of heart size, improvement of the renal function and a lower rate of cerebrovascular events [22]. However, the beneficial effects were counteracted by the severe orthostatic hypotension, and the evolution of antihypertensive drugs favored lumbar sympathectomy to be generally removed from medical practice in 1975.

Technique of Renal Sympathetic Denervation (RSDN)

Sobotka and Esler (pioneers in percutaneous renal artery sympathetic denervation) conducted the first studies of catheter-based renal ablation, using radio frequency energy. This procedure involves insertion of an endovascular catheter under fluoroscopic guidance through the femoral artery and its advancement towards a distal renal artery. Sympathetic nerve ablation was performed due to radiofrequency energy applied through an electrode located on the tip of the endovascular catheter. Thus, there were selective thermal injuries at the level of renal sympathetic nerves, while abdominal, pelvic and lower limbs nerves were not affected. Multiple radiofrequency treatments were applied circumferentially, initially in the distal renal artery, and then proximally with catheter withdrawal. The energy applied was lower than that used in electrophysiological studies on the heart; the entire

procedure lasting 30-60 minutes. Selection of patients to be subjected to RSDN is quite scrupulous.

Table 1 shows the main eligibility and exclusion criteria in all clinical studies conducted to date.

Table 1

Eligibility and exclusion criteria in RSDN clinical trials

Eligibility criteria	Exclusion criteria
1. Office SBP≥160mmHg (≥150mmHgin type 2 diabetes), when administering ≥3antihypertensives at maximum tolerated doses (including a diuretic).	1. Secondary hypertension 2. Pseudoresistence 3. Impaired renal function (GFR≤ 45 ml/min/1.73 m2) 4. Renovascular abnormalities: accessory arteries, renal artery stenosis, previous revascularization 5. Pregnancy 6. Type 1diabetes 7. The presence of permanent pacemaker or implantable cardioverter defibrillator 8. Myocardial infarction, unstable angina or stroke in the previous six months

Note: SBP - systolic blood pressure.

It is to be noted that the main renal artery must have a length ≥ 20 mm and have a diameter ≥ 4 mm to avoid structural damage to the arterial wall. Relative contraindications for performing RSDN include visible renal artery stenosis, calcification or atherosclerotic plaque and multiple renal arteries which supply the upper and lower poles of the kidney.

Renal artery denervation in patients with resistant hypertension, using a standard electrophysiology catheter, showed a significant reduction in blood pressure [23]. These data led to the development of numerous catheter systems that are under clinical evaluation. Currently, four systems used in radiofrequency ablation technology have been approved for phase III of the clinical trial in the US, Europe and other countries: Medtronic's Symplicity, St. Jude's EnligHTN, Boston Scientific's Vessix's V2 and Covidien's OneShot.

RSDN preclinical data

The importance of the renal sympathetic nervous system in hypertension has been suggested; when its increased activity was described in rats with spontaneous genetic hypertension compared with the normotensive control group [24]. Several animal models have been used to study the impact of renal sympathetic fibers on blood pressure [25].

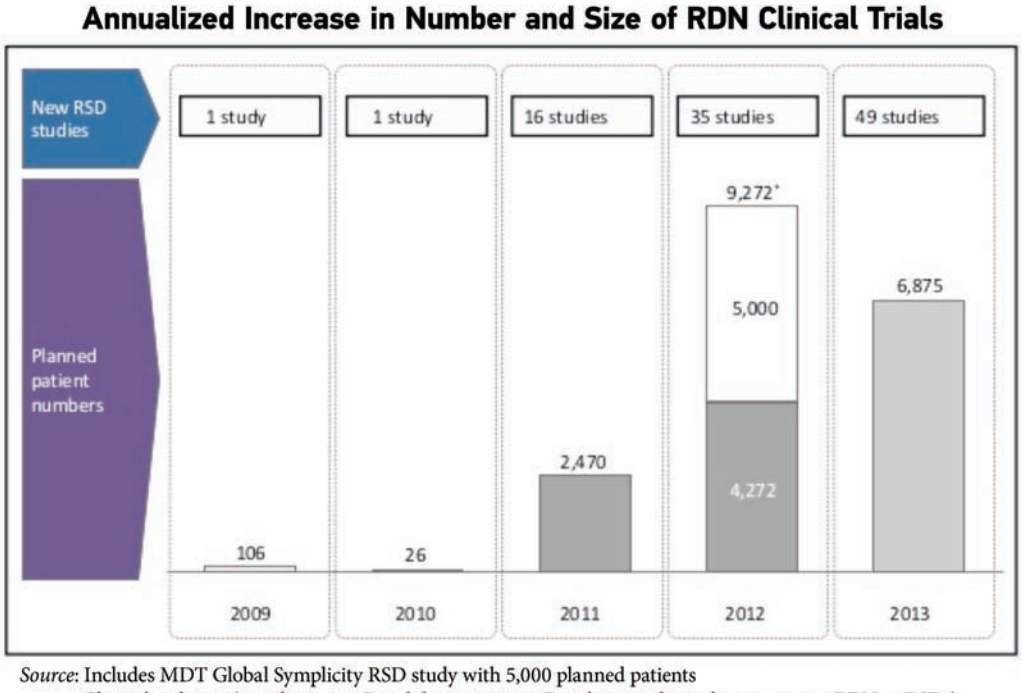
In a large research study including more than 300 pigs, a significant decrease ($p < 0.0001$) of noradrenaline in the kidney tissue was observed in animals subjected to renal denervation compared to the control group. The procedure safety was verified through angiography, as well as histopathologic and clinical data at 7, 30, 60, and 180 days. At all evaluation stages the endothelium was confirmed to be intact, while arterial stenosis was absent.

RSDN clinical trials

To show RSDN efficacy and safety, several clinical trials have been initiated. Thus, in 2009 a clinical trial including 106 patients was initiated; the number of initiated clinical trials reached 49 by 2013, and 6,875 patients were enrolled [26] (fig. 2).

The European Society of Cardiology has developed a Consensus on selection of patients to be subjected to RSDN [27] (fig. 3).

The largest and most important clinical trials according to data obtained are considered those conducted by Medtronic Company (fig. 4) [28].



Source: Includes MDT Global Symplicity RSD study with 5,000 planned patients
Clinicaltrials.gov (search terms: «Renal denervation», «Renal sympathetic denervation», «RDN», «RSD»)

Fig. 2. Annual share of RSDN clinical trials.

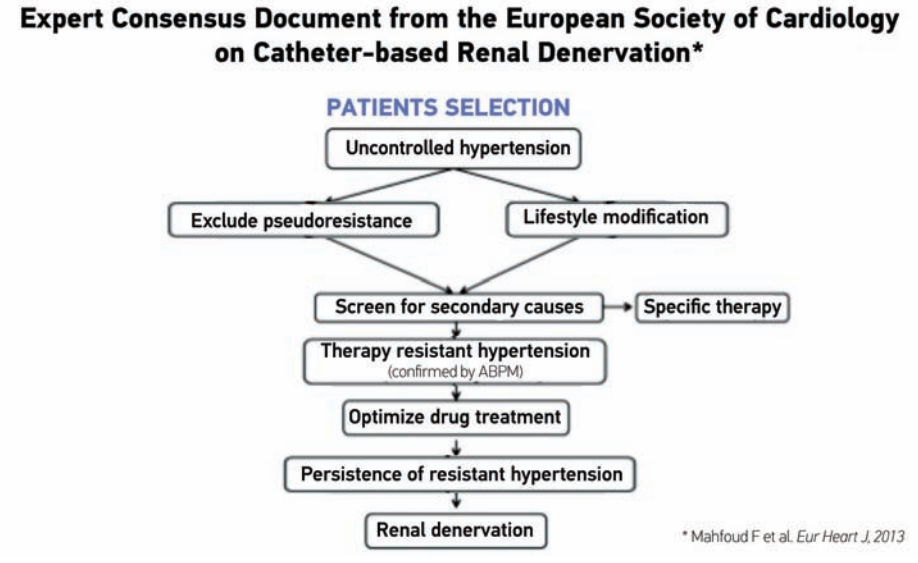


Fig. 3. Selection of patients to be subjected to RSDN.

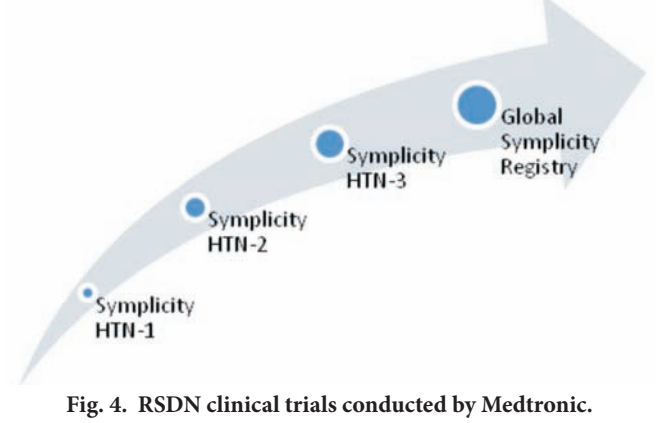


Fig. 4. RSDN clinical trials conducted by Medtronic.

Symplicity HTN-1. Symplicity HTN-1 was a series of pilot studies that included 153 patients. A decrease in blood pressure by -22/-10 mmHg at 6 months after procedure, and by -32/-14 mmHg at 36 months has been reported [29].

Symplicity HTN-2. Symplicity HTN-2 is the first randomized clinical trial including 106 patients with treatment-resistant hypertension, that showed a decrease in systolic and diastolic blood pressure by -32/-12 mmHg, the beneficial effect being maintained for 3 years [30].

Symplicity HTN-3. Symplicity HTN-3 was first blind randomized trial, the results of which were long overdue and veridically much higher than those obtained in previous studies, taking into account the exclusion of many limitations such as small number of the study lot, limited use of ambulatory blood pressure monitoring (ABPM), lack of the blind control lot, etc. After performing the initial screening, patients followed ambulatory treatment with constant blood pressure monitoring at home for 2 weeks.

At the next stage of evaluation, having confirmed treatment-resistant hypertension, renal angiography was performed. During the procedure, depending on the suitability of anatomical eligibility criteria, patients were randomized into two lots – control lot that continued to take medication over the next 6 months (primary end-point), and lot subjected to RSDN [31].

In March 2014, Symplicity HTN-3 trial results were published. They appeared to shatter hopes around renal denervation as a method for the treatment of resistant hypertension. The change in office SBP at 6 months was the primary efficacy end-point, while the change in SBP measured by ABPM was the secondary end-point. At 6 months follow-up, office SBP in patients subjected to RSDN decreased by 14.1 mmHg and by 11.7 mmHg in the control group. The difference of 2.39 mmHg, with p=0.26, was statistically insignificant. The change in ambulatory SBP at 6 months was 6.8 mm Hg in the denervation group and 4.8 in the control group. The difference between the two groups was 1.96, with p=0.98, being also statistically insignificant.

However, the study has reached the point of primary safety, major adverse effects being recorded in 5 patients (1.4%) in the denervation lot and 1 (0.6%) patient in the control lot [32]. This study showed no RSDN benefit, although it demonstrated its safety. These data contradict the data obtained in previous trials that have demonstrated a significant decrease in blood pressure after RSDN. The obvious question arose: why were the Simplicity HTN-3 trial results so different compared to the previous two studies.

Certain assumptions were issued, namely that patients were not adequately stabilized before randomization, given that some drugs require more than 8 weeks to achieve maximum effect and the follow-up in the study was only 2 weeks. Moreover, in this study 40% of patients used direct vasodilators and a higher percentage took spironolactone. The patient population included in the study constituted another difference. In Simplicity HTN-3 one third of subjects were African-American, while Caucasians predominated in previous studies, being recognized a more difficult response of African-American hypertensive patients to therapy. Other observations are related to the absence of randomization in HTN-1, and, though HTN-2 was randomized, it was not blind [33].

Symplicity Global Registry study

Symplicity Global Registry study including patients with resistant hypertension is underway. It collects data on other diseases characterized by increased activity of the SNS such as type 2 diabetes, heart and renal failure, obstructive sleep apnea, etc. Enrollment of 5000 patients to be subjected to RSDN is expected in 231 international centers in 37 countries. After presenting the Symplicity HTN-3trial results, which showed RSDN inefficacy compared to placebo, there are preliminary data obtained from the Symplicity Global Registry, demonstrating significant reductions in both office and ambulatory SBP after 6 months.

These data were presented at the scientific session of the American College of Cardiology on March 30, 2013 [34].

Conclusions

1. Despite the negative results of the Symplicity HTN-3 trial, it is too early to make conclusions that RSDN therapy failed in the management of resistant hypertension.

2. There are sufficient clinical data from multiple clinical trials demonstrating positive effects both in lowering blood pressure and other diseases associated with increased activity of the SNS.

3. A more rigorous selection of patients is necessary to perform RSDN**,** at present the procedure being recommended only for patients with resistant hypertension.

4. RSDN is not a "panaceea" in the treatment of patients with resistant hypertension.

5. Several large randomized clinical trials are necessary.

6. A cost-effectiveness analysis of RSDN would be welcome.

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