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# Renal Denervation Therapy for Resistant Hypertension

*Mark Davis, MD*
*Ernesto L. Schiffrin, MD, PhD*
*Dominique Joyal, MD*[*]

**Address**
[*]Department of Medicine, Division of Cardiology, Jewish General Hospital, McGill University, 3755 Cote Ste-Catherine Rd, Suite E-215, Montreal, Quebec H3T 1E2, Canada
Email: djoyal@jgh.mcgill.ca

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**Abbreviations** *ABPM* Ambulatory blood pressure monitoring · *BP* Blood pressure · *HTN* Hypertension · *dBP* Diastolic blood pressure · *MR* Mineralocorticoid receptor · *RCT* Randomized controlled trial · *RDN* Renal sympathetic denervation · *RF* Radiofrequency · *RH* Resistant hypertension · *sBP* Systolic blood pressure

## Opinion statement

Hypertension is common and leads to significant cardiovascular morbidity and mortality. Some patients are unable to achieve target blood pressures despite multiple antihypertensive medications; these patients are labeled as having resistant hypertension. To palliate the lack of pharmacologic options, recent technological advances led to the development of an interventional procedure to treat hypertension, namely renal sympathetic denervation. This percutaneous procedure involves the ablation of the afferent and efferent nerves surrounding the renal arteries. Many studies that were primarily observational in nature had very promising results. Systolic blood pressure reductions in the order of 25–30 mm Hg were observed in a series of unblinded studies, leading to the approval and widespread use of this technology across Europe, Australia, and Canada. However, a recent rigorous single blinded sham-controlled clinical trial failed to meet its efficacy endpoints. There are several postulated reasons for the conflicting results, which are discussed in this manuscript. These recent findings make us reflect on the need for rigorous clinical trials prior to the early approval and clinical adoption of novel technologies. At the moment, renal denervation remains an investigational procedure. Several trials are underway using different technologies, which, upon completion, will clarify the proper role of renal denervation for the treatment of patients with resistant hypertension.

## Introduction

Hypertension affects close to 30 % of the population worldwide [1]. It leads to significant cardiovascular morbidity and mortality and is associated with extensive health care costs [2]. Despite pharmacologic and lifestyle changes, many patients take three or more different classes of antihypertensive medications (and in some cases more than five different medications) but yet fail to achieve target blood pressures. These patients, with resistant hypertension (RH) and limited pharmacologic treatment options are said to comprise between 5 %–30 % of the hypertensive population [3–6].

Renal sympathetic denervation (RDN), a percutaneous procedure involving the ablation of sympathetic nerves surrounding the renal arteries was shown to significantly reduce blood pressure in several observational and unblinded studies, findings that were not replicated in a recent blinded randomized controlled trial. These contradictory findings merit discussion with regards to possible explanations for the different results between the blinded and unblinded studies. Thus, the aim of this review is to discuss the evolution of RDN for the treatment of RH, its earlier and current evidence, and the envisioned direction of the field of RDN.

# Renal denervation

## Pathophysiology

Renal arteries are encased with both afferent and efferent sympathetic nerves that travel to and from the brain. When efferent sympathetic nerves are activated, constriction of the renal arteries occurs, which results in a decrease in glomerular filtration rate (GFR) and a subsequent increase in renin release [7–10]. This results in increased sodium and water reabsorption and increase in blood pressure (BP). The activation of the renal afferent sympathetic nerves results in signaling to the hypothalamus with further widespread increased sympathetic outflow [7–10]. Removing the afferent signaling from the kidney ultimately leads to a decrease in efferent renal sympathetic nerve signaling and decrease in total body sympathetic outflow. Given this intricate interaction, initial animal studies showed decreased sympathetic outflow and improved BP by damaging both afferent and efferent renal sympathetic nerves [7–9]. With this understanding, a percutaneous approach to ablate the sympathetic nerves surrounding the renal arteries was developed.

## Description of the technique

RDN is currently performed as a percutaneous procedure, under sedation. An intraducer sheath is inserted into the femoral artery in a fashion similar to that of coronary angiography. A catheter is advanced under fluoroscopic guidance to the ostium of the renal arteries. A renal artery angiogram is performed to ensure that the renal arteries have adequate anatomy for RDN. Typically arteries ≥4 mm in diameter and at least 20 mm in length are required. After accessing the renal artery, the ablation catheter is inserted for delivery of radiofrequency (RF) energy to the arterial wall.

Multiple different ablation catheters have been studied; the most commonly used worldwide being the SYMPLICITY catheter system (Medtronic, Minneapolis, MN). This catheter has a monopolar distal electrode for the delivery of RF ablation. The catheter is advanced into the renal artery proximal to the first branch and then 4-6 RF ablations separated by 5 mm are performed in a rotational fashion from the distal to proximal segments in both

the right and left arteries. Each individual ablation lasts approximately 120 s. Besides the achievement in an impedance threshold as measured by a console, no marker of successful ablation is known or available. The most frequent side effect is diffuse abdominal pain, managed by analgesia and/or increased sedation [10–12]. Other catheters, such as the Celcius ThermoCool catheter (Biosense Webster, Diamond Bar, CA) (typically used for RF ablation in electrophysiology) are used in a similar fashion. The EnligHTN (St. Jude Medical, St. Paul, MN) and Vessix (Boston Scientific, Natick, MA) catheter systems use RF energy but have electrodes mounted on a basket or balloon to allow for one single treatment with all areas ablated at the same time. The TIVUS (Cardiosonic, Tel Aviv, Israel) and PARADISE (ReCor Medical, Palo Alto, CA) systems use ultrasound technology through a percutaneous route to cause denervation.

## Complications of renal denervation

The procedural complications related to RDN are similar to those seen with typical coronary or peripheral angiography. The complication rate is less than 2 % and includes rare pseudoaneurysm formation at the site of arterial puncture as well as a few documented cases of renal artery dissection, or renal artery stenosis post-ablation [11–16]. In the recent SYMPLICITY HTN-3, there was no difference in the safety endpoints between the RDN and sham-treated patients as will be discussed further [18].

## Major studies and chronology of evidence

### SYMPLICITY HTN-1

Following an initial proof of principle study [12] using the first RDN catheter, Ardian (Mountain View, CA) funded the open label proof of concept study SYMPLICITY HTN-1[11]. This study enrolled 153 patients in 19 sites within Australia, Europe, and the United States. Patients were diagnosed as having RH on the basis of an average of three office systolic blood pressures (sBP) >160 mm Hg on≥three antihypertensive medications, of which one was a diuretic. Patients were followed for up to 2 years in the initial publication, with final data publishing 36-month changes in blood pressure. The decrease in blood pressure at 1, 3, 6, 12, 24 and 36 months were [expressed as decrease in sBP/decrease in diastolic blood pressure (dBP)] 20/10, 24/11, 25/11, 26/14, 32/14, 32/14, respectively. The procedure was safe with only one dissection of the renal artery away from the site of intervention and three pseudoaneurysms at the site of femoral artery access. No renal artery stenosis was noted on follow-up. There was a negligible decrease in GFR.

### SYMPLICITY HTN-2

Ardian subsequently funded SYMPLICITY HTN-2, a randomized, unblinded controlled study [14]. The same BP criteria to define RH were used to enrol patients in Europe, Australia, and New Zealand. A total of 52 patients underwent RDN and 54 patients served as controls. The initial study published 1, 3, and 6 months data. A follow-up study published 12-month results, but allowed for a crossover after 6 months [17]. The office BP of the

RDN group decreased by 20/7, 24/8, 32/12, and 28/10 mm Hg for 1, 3, 6, and 12 months, respectively, compared with controls.

Multiple sub-studies of the SYMPLICITY studies or case reports demonstrated promising results for end-organs pathologies affected by hypertension (HTN) following RDN. These include decrease in left ventricular hypertrophy [18], recurrence of atrial fibrillation post-ablation [19], ventricular storm [20], arterial stiffness [21], and insulin resistance [22, 23]. Yet all of these studies were based on small number of patients and most did not have a control population.

By 2010, Medtronic had purchased Ardian. The promising and consistent results of the SYMPLICITY studies led to the approval of RDN and the SYMPLICITY catheter system in Australia, Europe, and Canada. Since then, six other catheters have received CE approval for use in Europe: St. Jude Medical EnligHTN System, Boston Scientific (previously Vessix) V2 Renal Denervation System, Covidien OneShot System, Recor Paradise System, Terumo Iberis System (Leuven, Belgium), and Cordis RENLANE (Brigewater, NJ) Renal Denervation System. Multiple observational studies, some from the above devices, and from other non-approved devices yield similar promising results as the initial SYMPLICITY studies [11, 12, 14, 17, 19, 24–31].

A recent systematic review and meta-analysis of 18 unblinded studies confirmed the observed benefit of RDN on BP reduction. The pooled analysis showed that RDN led to a decrease in systolic and diastolic BP at 6 months of –29/–11 mm Hg and –25/–10 mm Hg for controlled and uncontrolled studies, respectively [13]. These effects were sustained beyond 24 months. No difference in BP reduction was seen with regards to different catheter type [14]. The overall nonresponder rate in the study population of 561 patients was only 13 %. Most of the studies analyzed reported on office BP (10/12 had office BP as the primary endpoint, whereas 2/12 studies had ambulatory blood pressure monitoring (ABPM) as a primary endpoint). Notwithstanding limitations of analysis of mostly observational studies, and short of a rigorous blinded randomized controlled trial, the body of evidence at the time suggested benefits in BP parameters from RDN.

## SYMPLICITY HTN-3

The SYMPLICITY HTN-3 study was designed as a prospective, single blinded, randomized sham-controlled trial. Hypertensive subjects had to be on three or more antihypertensive medications at maximally tolerated doses of different classes with at least one being a diuretic [32]. The primary and secondary endpoints were change in office and ABPM sBP at 6 months, respectively. Superiority margins were set at 5 and 2 mm Hg for office and ABPM sBP, respectively, as these cut-offs are associated with cardiovascular clinical impact in pharmacology trials. The primary safety endpoint was a composite of major adverse events defined as mortality, end stage renal disease, embolic events, renal artery perforation or dissection, vascular complications requiring intervention or blood transfusion, and hospitalization for hypertensive crisis or new renal artery stenosis. Medication changes during the 6-month follow-up period were only allowed if there was an adverse event, the patient was symptomatic, sBP dropped <15 mm Hg, or increased >15 mm Hg above baseline. The staff measuring the BP were blinded to the treatment group, as

were subjects. Patients were required to document home BP prior to follow-up, as well as to document medication compliance.

SYMPLICITY HTN-3 did not meet its primary or secondary efficacy endpoints [33••]. At 6 months, the sBP difference between the RDN (364 patients) and sham-treated (171 patients) groups was –2.39 mm Hg [CI –6.89 to 2.12; $P$=0.26] [33••]. The change in 24-h ABPM difference between RDN and the sham-treated groups was –1.96 mm Hg [CI –4.97 to 1.06; $P$=0.98]. Hence, the superiority margins of 5 mm Hg for office sBP and 2 mm Hg for 24-h ambulatory sBP were not achieved. The safety endpoint was met, however, because no significant difference in complication rate was noted between the groups.

## Possible explanations for the discrepancy in results between the unblinded and blinded studies

The findings of SYMPLICITY HTN-3 raise several issues, both on the predicted accuracy of unblinded studies and on clinical application and approval of new technologies based on those studies. Rarely have we seen such a discrepancy in results upon the publication of a rigorous blinded study. In essence, the results of SYMPLICITY HTN-3 are surprising for two reasons: the smaller expected magnitude of sBP reduction in the RDN group and the larger expected sBP reduction in the sham-treated group. Several hypotheses may explain these observations, which will need to be considered for future RDN studies.

First, the most obvious difference between the initial studies and SYMPLICITY HTN-3 is the inclusion of a sham-treated group, representing the "placebo" group. The significant reduction in sBP in the sham-treated group (–11.74±25.94 mm Hg, $P$<0.001) suggests the presence of the placebo effect. Hence, the negative results of this trial are due in part to the similar magnitude of sBP reduction between RDN and sham-treated groups, both being statistically significant. Other sham-controlled interventional trials have led to negative results [34], but rarely is it derived from such a profound effect in the sham-treated group. Interestingly, the placebo effect usually refers to a *perceived* improvement in a medical condition. BP being, in most case, a silent marker, the mechanism for this non-subjective marker decrease remains unclear. It is possible that with patients believing they had RDN, their own lifestyle, anxiety, and other individual factors affecting BP were modified. Regardless of the reasons, which will need to be explored, the placebo effect appears to have played an important role in this trial.

Another explanation for the significant effect in the sham-treated group is the observer effect, also known as the Hawthorne effect. Initially described on factory workers, it refers to a phenomenon where workers, or patients, modify an aspect of their behavior in response to a change in their environment (ie, being observed or studied. In medical trials, this may be manifested by patients adopting healthier behavior, leading to improvement in a medical condition. In the case of hypertension, one can speculate on healthier lifestyle changes or simply better medication compliance during the trial period.

Other possibilities are related to the smaller effect size in the RDN group, compared with prior unblinded studies. In the initial proof of principle study, effective renal denervation was confirmed by a decrease in norepi-

nephrine spillover [12]. Furthermore, studies conducted as extensions of SYMPLICITY HTN-2 documented substantial reductions in muscle sympathetic nerve activity confirming effecting denervation and decreased central sympathetic outflow [35, 36]. In SYMPLICITY HTN-3 there were no measures to ensure effective denervation. Besides reaching an impedance threshold, there is no immediate marker of successful denervation with the current technology, as previously mentioned. A hypothesis is raised as to whether similar effective denervation was reached compared with earlier SYMPLICITY studies. Indeed, many of the operators were performing the procedure for their first time. Of the 111 operators in the study, 34 only performed one procedure. Yet, in supplementary data analysis, there was no difference in the change in sBP comparing operators performing<five to≥five procedures.

Another potential reason for the diminished efficacy in the RDN group is the rigorous patient selection. In all previous studies, patients were enrolled based on a set of three office BP measurements taken at the same visit, without further confirmation. Thus, if patients had a higher than normal blood pressure that day, they preferentially would be included in prior studies [37]. In SYMPLICITY HTN-3, patients were selected based on an office BP result, but required home BP readings to be confirmed and an ABPM sBP ≥135 mmHG. Documented compliance of their medication regimen was required before inclusion in the study [33••]. This resulted in the exclusion of patients who may have had a supra-normal BP during their clinic visit, but otherwise had controlled BP values on ABPM [38]. The other key difference in this study is that medication compliance was ensured based on patient diaries [33••]. Although previous studies did warrant there were no medication changes in the month to three months prior to enrolment, there was no active process to guarantee medication compliance prior to or during the studies. Regression to the mean likely played a role explaining why unblinded and observation trials, where patient selection may not have been as rigorous, demonstrated exaggerated sBP response. Recently, Persu et al., who looked at subject level data for RDN, found that there is a highly variable response to RDN, and that most of the results seen in trials suggest a large regression to the mean response that will also be seen with the addition of a subsequent antihypertensive agent [2].

Differences in medical regimen between the studies also deserve mentioning. In SYMPLICITY HTN-3 there was a greater percentage of patients in both the RDN and the sham-treated group using mineralocorticoid receptor (MR) blocker therapy compared with the previous SYMPLICITY studies, as depicted in Table 1. The addition of MR blockade (spironolactone or eplerenone) often results in significant BP reduction leading to adequate BP control. Consequently, RDN applied in the context of improved MR blockade may have been less effective than that seen in previous studies. This raises the question if the definition of RH, and as an extension defining patients who are potential candidates for RDN, should include adequate treatment with specific antihypertensive medications, including a renin-angiotensin system (RAS) blocker, a calcium channel blocker (CCB), a potent diuretic (chlorthalidone or indapamine), plus a MR blocker. Some patients may not tolerate this combination therapy and can thus be defined as having RH on the basis of the inability to control BP with adequate BP-lowering medications, whereas others, even with this regimen, may not be able to achieve an adequate BP response. Since these rigorous selection

**Table 1. Comparison of the three Symplicity trials**

| | SYMPLICITY HTN-1 | SYMPLICITY HTN-2 | | SYMPLICITY HTN-3 | |
|---|---|---|---|---|---|
| Study Design | Open-label observational | Randomized control trial | | Randomized sham-controlled study | |
| BP requirement | Office≥160 mm Hg | Office sBP≥160 mm Hg, or≥150 mm Hg if T2DM. | | Office and home sBP≥160 mm Hg & ABPM sBP >135 mm Hg | |
| Antihypertensive Requirement | – ≥3 different classes (including a diuretic), at target or max doses | – As Symplicity HTN-1, with documented compliance for 2 weeks | | – As Symplicity HTN-1 and no changes in medications in the two weeks prior to enrolment<br>– Confirmed medication compliance by diary | |
| Exclusion Criteria | – eGFR<45 ml/min per 1.73 m2<br>– T1DM<br>– Known secondary cause of HTN | – eGFR<45 ml/min per 1.73 m2<br>– T1DM<br>– Contraindications to MRI<br>– Severe valvular stenosis<br>– Pregnancy<br>– History of MI, UA, CVA in past 6 months<br>– Renal artery<4 mm diameter or <20 mm length or accessory artery | | – Secondary causes of hypertension<br>– eGFR<45 ml/min per 1.73 m2<br>– T1DM<br>– >1 hospitalization for hypertensive emergency in previous year<br>– Renal artery stenosis>50 %<br>– Renal artery aneurysm<br>– Prior renal artery intervention<br>– Multiple renal arteries<br>– Renal artery diameter<4 mm<br>– Renal artery length<20 mm | |
| Medication alterations | Allowed | Allowed (if medically required) | | Allowed (if medically required) | |
| | | RDN | Control | RDN | Sham |
| # of Patients | 153 | 52 | 54 | 364 | 171 |
| Age | 57±11 | 58±12 | 58±12 | 58±10 | 56±11 |
| Sex (Female) | 39 % | 35 % | 50 % | 51 % | 36 % |
| T2DM | 31 % | 40 % | 28 % | 47 % | 41 % |
| CAD | 22 % | 19 % | 7 % | 28 % | 25 % |
| Hyperlipidemia | 68 % | 52 % | 52 % | 69 % | 65 % |
| eGFR ( ml/min per 1.73 m2) | 83±20 | 77±19 | 86±20 | 73±16 | 74±19 |
| Baseline BP (mm Hg) | 176/68±17/15 | 178/97±18/16 | 178/98±16/17 | Office: 180/97±16/17<br>Home: 169/90±16/16<br>ABPM: 159/88±13/14 | Office:180/99±17/16<br>Home: 169/93±16/16<br>ABPM:160/91±15/14 |
| # of antihypertensives | 5.1±1.4 | 5.2±1.5 | 5.3±1.8 | 5.1±1.4 | 5.2±1.4 |
| Aldosterone Antagonist | 22 % | 17 % | 17 % | 23 % | 29 % |
| ACEI or ARB | 91 % | 96 % | 94 % | 99 % | 95 % |
| Direct Renin Inhibitor | 14 % | 15 % | 19 % | 7 % | 7 % |
| Beta blocker | 82 % | 83 % | 69 % | 85 % | 86 % |

**Table 1.** (Continued)

| | SYMPLICITY HTN-1 | SYMPLICITY HTN-2 | | SYMPLICITY HTN-3 | |
|---|---|---|---|---|---|
| CCB | 75 % | 79 % | 83 % | 70 % | 73 % |
| Centrally acting sympatholytic | 33 % | 52 % | 52 % | 49 % | 44 % |
| Vasodilator | 19 % | 15 % | 17 % | 37 % | 45 % |
| Alpha 1 blocker | 19 % | 33 % | 19 % | 11 % | 14 % |
| Results | | | | | |
| Change in office sBP at 6 months (mm Hg) | -25±23.7 (*P*P<0.0001 vs baseline) | -32±23 (*P*<0.0001 vs baseline, *P*P<0.0001 vs control) | 1±21 (*P*=0.77 vs baseline) | -14±24 (*P*P<0.001 vs baseline, *P*=0.26 vs sham) | -12±26 (*P*<0.001 vs baseline) |
| Change in ABPM sBP at 6 months (mm Hg) | N/A | -11±15 (*P*=0.006 vs baseline) | -3±19 (*P*=0.51 vs baseline) | -7±15 (*P*<0.001 vs baseline, *P*=0.98 vs sham) | -5±17 (*P*P<0.001 vs baseline) |

*ABPM* ambulatory blood pressure monitoring, *ACEI* angiotensin converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *BP* blood pressure, *CAD* coronary artery disease, *CCB* calcium channel blocker, *CVA* cerebrovascular accident, *eGFR* estimated glomerular filtration rate, *HTN* hypertension, *MI* myocardial infarction, sBP systolic blood pressure, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus, *UA* unstable angina

criteria were not used in original studies, their RDN groups may have been rendered more responsive to therapy, and their comparator groups less sensitive to the placebo effect.

A recent, albeit small study, enrolled patients with true treatment RH after excluding patients with confounding poor drug adherence or spurious hypertension [39]. Prior to randomization, initially eligible participants were tested for white coat hypertension, thoroughly assessed for secondary causes, observed taking their medications, and had their home BP measured to assess normalization. This resulted in 2/3 of potential candidates being excluded to select a truly resistant population. The study was stopped early, as drug treatment was superior to RDN in patients with true RH.

Thus, the reasons for the lack of efficacy of RDN in SYMPLICITY HTN-3 trial appear multifactorial. There may be subgroups that derived a lesser benefit from the procedure. It has been suggested that one such group might be the African-American hypertensive population, but this remains, at this point, speculative. As for whether other devices/catheters yield better outcome also remains unproven. So far, only the SYMPLICITY catheter has been tested in a rigorous trial, and its associated outcome data must be considered the most valid reference to date.

## Terminated and ongoing studies

SYMPLICITY HTN-4, planning to evaluate RDN in a moderate HTN population with office sBP of 140–160 mm Hg, has been suspended. The EnligHTN IV study testing the multi-electrode RDN system has been stopped at its very beginning; the trial was halted because of concerns about slow enrollment. The only studies that are currently enrolling patients, or plan to enrol patients, are those employing a different RDN catheter, or are examining a specific sub-population via the SYMPLICITY system. These include ALLEGRO-HTN (NCT01874470), which uses the ALLEGRO catheter, HTN-J (NCT01644604) using the MDT-2211 system, ACHIEVE (NCT01789918) and REALISE (NCT01529372) using the PARADISE system, REDUSE-HTN (NCT01541865) using the Vessix system, RDN+AF (NCT01907828 ) using the EnligHTN catheter, ReSET-2 (NCT01762488) using the same catheter and measuring 24-h ABPM, EnligHTN-II (NCT01705080), SoundITV (NCT01865591) using the Sound TX system, and SAVE (NCT01628198) and RELIEF (NCT01628172) using the Celcius Thermocool catheter. There are also many subpopulation studies that are still using the SYMPLICITY catheter system to see its effect in Type 2 diabetes mellitus, renal failure, heart failure, atrial fibrillation, ventricular tachycardia, acute coronary syndromes, and stroke.

## Perspective

BP control is extremely important in preventing cardiovascular morbidity and mortality. RH is an important clinical challenge, but true RH may represent a smaller proportion than initially thought. RDN is based on sound pathophysiology, appears safe and, although invasive, is technically simple and non-challenging. However, it was not effective when tested in a rigorous blinded sham-controlled clinical trial. This is in contrast to the multitude of positive observational studies. Clinicians must then reflect on the early adop-

tion of novel procedures and regulatory authorities on early approval of novel devices, without proper large rigorous clinical trial support. Whether other devices will prove to be effective will depend on completion of future sham-controlled clinical trials, ideally of similar quality to SYMPLICITY HTN-3.

# Conclusions

RDN, in light of recent clinical trial data, remains an investigational procedure for the treatment of RH. Further large high-quality clinical trials are needed before wide adoption of RDN for clinical use.

## Compliance with Ethics Guidelines

**Conflict of Interest**

Dr. Mark Davis and Dr. Ernesto L. Schiffrin each declare no potential conflicts of interest. Dr. Dominique Joyal reports personal fees from AstraZeneca, EliLilly, and Boston Scientific.

**Human and Animal Rights and Informed Consent**

This article does not contain any studies with human or animal subjects performed by any of the authors.

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