Renal Sympathetic Denervation Therapy in Hypertension

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Abstract

Sympathetic nervous system plays an important role in the pathogenesis of hypertension. In resistant hypertension, when pharmacotherapy fails, there may be a place for renal sympathetic denervation. Though initial studies showed promising results, sham controlled studies proved negative. However, learning lessons from the previous trials, recent studies probably with better design and methodology seem to be resurrecting renal sympathetic denervation therapy for resistant hypertension.

Key words: Resistant hypertension, Sympathetic nervous system, Renal sympathetic denervation

Introduction

Hypertension (HTN) is among the most prevalent chronic illness around the world and a powerful risk factor for cardiovascular events and chronic kidney disease. Globally, HTN affects approximately one in four adults and results in over 10 million deaths annually. Among patients with HTN, around 50% do not meet treatment targets and about 10–20% of these uncontrolled hypertensives have what is called as resistant HTN. The prevalence of resistant HTN ranges approximately from 5% in general medical practice to 50% in nephrology clinics. Resistant HTN is defined as blood pressure that remains above goal despite concurrent use of three antihypertensive agents of different classes, one of which should be a diuretic, in their optimal or maximal tolerated doses. Patients whose blood pressure is controlled with four or more medications are also considered to have resistant HTN.

Such individuals are more likely to suffer from cardiovascular events and have a poor outcome compared to people whose BP is under control. Therefore, despite the availability of various classes of antihypertensive drugs, the need to control HTN further led to the discovery of various interventional measures including renal denervation therapy (RDN).

What is Renal Sympathetic Denervation?

It is a minimally invasive procedure during which an intra-arterial catheter is placed in the renal artery lumen and radiofrequency or ultrasonographic energy or a chemical agent is used to ablate the renal sympathetic nerves present in the vascular adventitia, thereby reducing the renal sympathetic efferent and sensory afferent signaling to and from the kidneys. However, before doing the procedure, it is important to establish anatomical suitability, with renal artery length >20 mm and diameter >4 mm considered ideal. The presence of renal artery stenosis, calcification, and plaques is relative contraindications for this procedure. As the nociceptive C fibers are colocated with the sympathetic nerves, it is important to ensure adequate analgesia and sedation throughout the procedure. Aspirin 75–100 mg per day is recommended for up to 4 weeks post-procedure.

Pathophysiology

Numerous studies have shown that sympathetic nervous system plays a key role in the development and progression of HTN and various other cardiovascular diseases. The afferent nerves from the kidney connect with the hypothalamus in the brain, which hosts various centers involved in regulating the autonomic nervous system. The efferent sympathetic activity, in turn, leads to renin release, systemic vasoconstriction, and sodium and water retention contributing to HTN [Figures 1 and 2].

Patient selection

Before recommending the procedure, it is important to carefully select the patient who is likely to benefit from it. Initial studies...
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were in patients with resistant HTN.\textsuperscript{[6-10]} Now, there are studies in patients with no background antihypertensive therapy and also along with antihypertensive therapy.\textsuperscript{[11-13]} There is also a recent study which reported the comparison in efficacy between different modalities of denervation.\textsuperscript{[14]}

The following criteria have been suggested when RDN was tried in patients with resistant HTN:

- Office BP >160 mmHg or >150 in type 2 diabetic patients
- ≥3 antihypertensive drugs in adequate dose including a diuretic
- Confirm adherence to medications
- Exclude secondary HTN and pseudo-resistant HTN
- Glomerular filtration rate >45 ml/min
- Suitable renal artery anatomy.

\textbf{Clinical Data}

Many trials have been conducted to study the effect of RDN in controlling HTN.

\textbf{Positive studies}

In a multicenter safety and proof-of-principle cohort study titled “Catheter-based renal sympathetic denervation for resistant HTN,”\textsuperscript{[6]} 45 patients of resistant HTN were studied and were followed up to 1 year. The study concluded that RDN caused significant and sustained blood pressure reduction, with no adverse events, in patients with resistant HTN. It also showed mean reduction of 47\% in renal noradrenaline spillover.

Following this study of 45 patients and adding some more patients in a nonrandomized fashion, an open-label study looked at the durability of blood pressure reduction out to 24 months in 153 patients.\textsuperscript{[7]} The procedure was without complication in 97\% of patients and RDN resulted in a significant reduction in BP and the effect was sustained up to ≥2 years of follow-up, and there were no significant adverse events.

Subsequent to this open-label study, 11 patients of 153 were followed up to 36 months.\textsuperscript{[8]} At 36 months, there was significant reduction in SBP and DBP. A reduction of 10 mmHg or more was seen in 93\% at 36 months. There was one new renal artery stenosis requiring stenting and there were three deaths unrelated to RDN occurred during follow-up.

SIMPLICITY HTN-2 was a multicenter, prospective RCT, and a larger study.\textsuperscript{[9]} It included 106 patients randomized in 1:1 fashion to RDN with standard medical treatment versus standard medical treatment alone. Primary end point was 6 months office

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Integration of sympathetic afferent and efferent activity in regulation of blood pressure. (a) Afferent renal sympathetics, (b) efferent sympathetic activation}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Actions of renal sympathetic activation}
\end{figure}
BP. Between-group differences in blood pressure at 6 months were 33/11 mmHg (P < 0.0001). Thus, this study showed significant reduction in BP compared to controls and 84% patients in the RDN group had >10 mmHg reduction in systolic BP. No serious adverse events were reported.

These trials so far were quite encouraging.

**Sobering studies**

However, then came SIMPLICITY-HTN 3, a sham study[10] which dampened the enthusiasm of those who reveled in RDN. It was an RCT, blinded, and parallel study that enrolled 535 patients with a mean age of 57 years, who were randomized in 2:1 manner to RDN or a sham procedure. Primary end point was changed in office systolic BP at 6 months and secondary end point was changed in 24 h ambulatory BP monitoring (ABPM). This study failed to show efficacy of RDN over sham procedure. It concluded that RDN was not superior to sham procedure and medical treatment in reducing office and ambulatory BP at 6 months in patients with resistant HTN.

A Cochrane review[15] looked at 1149 patients from 12 studies. The authors concluded, “in patients with resistant HTN, there is low-quality evidence that RDN does not change major cardiovascular events and renal function. There was moderate quality evidence that it does not change blood pressure and low-quality evidence that it caused an increase of bradycardia episodes.” They suggested that future trials should have a larger sample size, standardized procedural methods, longer follow-up, and hard clinical endpoints.

A meta-analysis by Fadl et al.[16] which included 5652 patients from seven major trials of RDN sounded a similar note. 985 patients were randomized to control (n 397) or RDN with SYMPLICITY™ catheters (n 588). Follow-up was for 6 months. The study concluded that, in selected patients of resistant HTN on antihypertensive drugs, RDN with the SYMPLICITY systems did not significantly decrease BP, but the procedure was safe. The authors suggested that future trials should make an effort to identify responders among hypertensive patients with evidence of sympathetic nervous overactivity.

**Discrepancy between the study results**

Prior studies[6-8] were non-randomized and compared the treatment results with baseline observations rather than with the results in a control group. Without a control group, the observed beneficial effect may have been a result of a close follow-up the patients received (i.e., the Hawthorne effect). SIMPLICITY-HTN 2 trial[9] lacked blinding and that is likely to introduce bias. The other limitations of the SIMPLICITY-HTN 2 trial[9] were probably unrecognized cases of white coat HTN and secondary HTN. The SIMPLICITY-HTN 3 trial[10] was a sham-controlled study and underscores the importance of conducting blinded trials with sham controls of a strategy before their clinical adoption. The SIMPLICITY-HTN 3 trial[10] clearly established an important placebo effect on results.

**New studies: New era and ray of hope for RDN**

After learning lessons from the previous trials in aspects of methodology, devices, and techniques, more studies on RDN were carried out, rolling out positive results, and resurrecting RDN in a way.

A randomized control trial, the RDN for HTN trial,[17] where 106 patients of resistant HTN were randomized, showed the superiority of RDN in combination with optimized pharmacotherapy compared with pharmacotherapy alone.

The PRAGUE-15 study[18] a randomized, open-label trial in 106 patients documented similar effects between RDN and optimized pharmacotherapy (mainly by adding spironolactone) with respect to BP-lowering efficacy; however, the pharmacotherapy was associated with more side effects and high discontinuation rates.

RCT-SPYRAL-HTN-OFF MED[11] In this study, 353 patients were screened. 80 patients were randomly assigned to RDN (n = 38) or sham control (n = 42) and followed up for 3 months. The efficacy of RDN was studied in the absence of antihypertensive medications, and it showed that office BP and 24 h ABPM reduced significantly from baseline to 3 months in the RDN group compared to control group and gave a biological proof of principle for the blood pressure-lowering efficacy of RDN. There were no major adverse events.

RCT-SPYRAL-HTN-ON MED[12] an international, randomized, single-blind, sham control, and proof-of-concept trial studied patients with uncontrolled HTN (aged 20–80 years) on antihypertensive medications and they included drug adherence testing also.

467 patients were screened and enrolled and the analysis of the first 80 patients randomly assigned to RDN (n = 38) and sham control (n = 42) was reported.

The reduction in blood pressure was significantly greater at 6 months in the RDN group than the sham control group for office systolic blood pressure, 24 h systolic blood pressure, office diastolic blood pressure, and 24 h diastolic blood pressure.

The study concluded that RDN in the main renal arteries and branches significantly reduced blood pressure compared with sham control with no major safety events. However, it was noted that incomplete medication adherence was common.

RADIANCE-HTN SOLO[13] study examined the treatment effect of the paradise RDN system (ReCor Medical) using ultrasound energy in hypertensive patients not on antihypertensive medication (daytime ambulatory blood pressure >135/85–<170/105). In this trial, RDN was by performing a circumferential ablation of the renal artery using ultrasound energy. Approximately two–three ablations lasting 7 s were delivered to each main renal artery. Here, too, the sham control strategy was followed.

The advantage of ultrasound energy is that it is able to be targeted to a specific depth.

At 2 months, treatment with RDN reduced daytime ambulatory systolic blood pressure to a greater extent than was observed in the sham arm. Overall, 20% of those who underwent RDN had
a daytime ambulatory blood pressure of <135/85 mmHg in the absence of antihypertensive medication. In addition, 24% had a 24-h ambulatory blood pressure <130/80 mmHg without medication. Comparatively, just 3% of patients in the sham arm achieved either of these treatment targets.

Three-arm randomized trial of different RDN devices and techniques in patients with resistant HTN,[14] this trial compared the effectiveness of three different strategies for RDN among patients with resistant HTN. 120 patients were randomized to RDN of the main renal arteries (RFM-RDN) (n = 39) versus radiofrequency ablation of the main renal arteries, side branches, and accessories (RFB-RDN) (n = 39) versus endovascular ultrasound-based RDN of the main renal artery (USM-RDN) (n = 42). Duration of follow-up was 3 months, mean patient age was 63.5 years, and 31% were females. It showed that among patients with resistant HTN, RDN using the paradise endovascular ultrasound RDN system resulted in a greater reduction in ambulatory SBP at 3 months compared with radiofrequency ablation of the main renal artery alone, but not over radiofrequency ablation of the side branches in addition to the main artery.

What do the Guidelines Say?

ACC/AHA guidelines[19] state that “several studies have investigated devices that interrupt sympathetic nerve activity (carotid baroreceptor pacing and catheter ablation of renal sympathetic nerves); however, these studies have not provided sufficient evidence to recommend the use of this device in managing resistant HTN. In particular, two RCTs of renal sympathetic nerve ablation have been negative.

ESC/ESH guidelines[20] state that “use of device-based therapies is not recommended for the routine treatment of HTN, unless in the context of clinical studies and RCTs, until further evidence regarding their safety and efficacy becomes available.” These guidelines were published before the present series of positive studies in favor of RDN. It appears that RDN has staged a comeback and is likely to find a place it deserves in the future guidelines.

Role of RDN

Role of RDN could be traced back to the years 1935–1960 when surgical sympathectomy was the treatment for malignant HTN and was found to be beneficial.[21] Although it improved survival and reversed target organ damage, it had to be discontinued due to disabling side effects such as hypotension and syncope.

RDN has a sound physiologic, pathophysiologic, and anatomic basis to be a therapeutic procedure for HTN. There are some questions to be answered in this interesting field of RDN:[22]

1. Are there predictors for responders?
2. Are there any intraprocedural feedbacks to inform the effectiveness of the sympathetic denervation?
3. Although researchers feel that BP reduction is an excellent surrogate marker, clinicians would like to have its effect on hard cardiovascular endpoints.

Conclusion

RDN as a form of treatment for HTN has gone through ups and downs. The present studies seem to be resurrecting RDN strategy in a select group of hypertensive patients. It is a minimally invasive percutaneous procedure and has established its safety, efficacy, and durability. It is likely to find a place in our therapeutic armamentarium and in guidelines in near future.

References


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