



Editorial Cardiovascular

Renal Denervation Therapy: The Spiral on a Straight Road

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Hypertension is a major global public health issue due to its high prevalence and its significant role in morbidity and mortality. Globally, hypertension contributes 12.8% of mortality, with over 1 billion affected.^[1] Notably, 82% of these patients reside in underdeveloped nations with India accounting for approximately 220 million adults.^[2] It is estimated that 46% of adults with hypertension are unaware of their condition. Only about 1 in 5 (21%) adults with hypertension have their condition under control.^[3] Blood pressure (BP) control rates remain disappointingly low, at only 23% among females and 18% among males.^[2] Several factors contribute to poor BP control, including treatment non-compliance, social isolation, psychiatric disorders, adverse reactions, and the multiple therapeutic regimens.^[4]

Renal denervation (RDN) is a catheter-based procedure designed to treat high BP by targeting the renal and systemic sympathetic nervous systems. This technique disrupts the sympathetic nerve endings in the outer layer of the renal arteries. Research has shown that RDN does not present higher risks than those found in control patients, with most risks related to femoral artery catheterization.^[5]

The ideal candidates for RDN are identified through a careful consideration of the risk-benefit balance, focusing on patients with the greatest clinical need. Shared decision-making is crucial in determining appropriate treatment options. At present, the patients with resistant hypertension and patients who cannot tolerate additional medications or unwilling for RDN can be considered to undergo this procedure.^[6] Priority patients should be given to impending stroke, recurrent transient ischemic attacks, and patients with heart failure and chronic kidney disease in whom BP reduction benefits the most especially their estimated glomerular filtration rate (eGFR) over 40 mL/min/1.73 m². This therapy is at present not recommended in kidney transplant patients and stage renal disease.^[7]

The era of RDN has come to the forefront over the past decade, despite experiencing numerous setbacks. However, there always seems to be light at the end of the tunnel. Initially, the promising results from SIMPLICITYHTN I and II suggested that we might finally have a solution to a problem affecting almost a third of the world's population. Yet, our jubilation was short-lived. The results of SIMPLICITY HTN III, the first sham-controlled trial, indicated that RDN therapy might have failed. Subsequently, extensive thought, innovation, and redesign ensued.

We realized that since the nerves arborize distally after the main renal arteries in most patients, distal ablation in the branch renal arteries might be necessary. In addition, many patients had accessory renal arteries that were not ablated, leading to insufficient BP reduction. The initial straight catheter design often failed to make contact with the vessel wall, resulting in unsuccessful

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ablation. Considering these points, several modifications were made: the catheter design was changed to a spiral shape with four electrodes to enhance contact and ablation effectiveness. It was also decided to ablate accessory renal arteries and branch renal arteries larger than 3 mm outside the renal shadow.

The results from SPYRAL HTN ON MED, SPYRAL HTN OFF MED, and the GSR registry have shown very promising outcomes. We have observed significant improvements in BP in denervated patients. An analysis from the extended GLOBAL SIMPLICITY DEFINE registry, which included 2872 patients (42% women), showed no significant difference in BP reduction between women and men. The office systolic BP reduction was -18.4 for women and -15.5 for men ($P = 0.13$), and the ambulatory 24-h systolic BP reduction was -8.8 for women and -9.3 for men ($P = 0.14$).^[8]

Malik *et al.*^[9] conducted a study on ten patients (seven females and three males) including one Indian patient, who underwent percutaneous radiofrequency catheter-based RDN between May 2012 and December 2013, with follow-ups ranging from 1 month to 18 months. At baseline, the treated patients had a mean office BP of 171.1/93.9 mm Hg (standard deviation [SD] 10.5/10.8) and were on an average of 4.2 antihypertensive medications. Their eGFR was 50.57 mL/min/1.73m² (SD 24.94). Following the procedure, office BPs were reduced by $-26.9/-9.7$, $-31.2/-14.1$, $-29.5/-11.87$, $-40.2/-12.4$, and $-37.2/-12.2$ mm Hg at 1, 3, 6, 12, and 18 months, respectively. There were no periprocedural complications or adverse events during the follow-up period. The study concluded that RDN is a safe and effective treatment, resulting in significant and sustained reductions in BP without serious adverse events in patients with treatment-resistant hypertension.^[9]

However, does this mean we have arrived at a definitive solution? Can we now offer RDN to all hypertensive patients with assured results? The answer is no. There are still many gray areas. At present, RDN is only offered to patients with resistant hypertension, and about 20% of patients are non-responders. We generally observe a better response in patients with higher sympathetic drive and higher heart rates. There is no on-table endpoint for denervation, and sometimes the effects take weeks to manifest. Nevertheless, RDN is an always-on therapy that works continuously, day and night.

At present, RDN is a cutting-edge catheter-based procedure for uncontrolled hypertension patients. It can be used alongside drug therapy and lifestyle modifications to optimize hypertension management. Studies have also explored RDN in conditions where it may offer benefits beyond BP reduction, such as heart failure, arrhythmias, and metabolic syndromes. Although RDN's has historical potential for managing resistant hypertension, there are challenges such as economic disparities, and limitations in health-care infrastructure. The future of RDN depends on continuous

research with a focus on evaluating its safety, efficacy, and patient outcomes through clinical trials and registries. For now at least, it offers a detour from the old and known simple drug therapies like "A Spiral on a Straight Road."

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