Renal denervation therapy for hypertension: still on trial

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Hypertension remains the leading risk factor for death and disability worldwide and affects one in three adults in the UK. Despite current management, primarily focusing on lifestyle modification and pharmacological therapies, up to a third of patients do not reach current blood pressure (BP) targets. Treatment-resistant hypertension (TRH: defined as having a BP above goal despite concurrent use of three antihypertensive agents of different classes, one of which should be a diuretic) is common, affecting around 6%-8% of people with treated hypertension in the UK. The reasons for treatment failure are wide ranging but poor adherence is a very major factor. For this reason, a once-only therapy to reduce BP in the long term is a very attractive option.

Renal denervation (RDN), as a treatment for hypertension, initially gained traction early this century. It is based on a sound pathophysiological understanding of hypertension and the role the sympathetic nervous system plays. Indeed, prior to the advent of modern antihypertensive therapies surgical sympathectomies were commonly used in the treatment of severe hypertension, although side effects were often intolerable. RDN differs from the earlier blunt approaches by directly targeting the renal sympathetic nerves, which are known to have an important role in regulating renal blood flow and sodium homeostasis. Theoretically, this should improve BP control, with reduced reliance on pharmacological therapies and without the side effects seen with surgical sympathectomy.

Initial studies using radiofrequency ablation of the renal sympathetic nerves in patients with TRH appeared to support this view, with substantial reductions in BP following the intervention. Indeed, at this stage some were describing RDN as a potential ‘cure’ for hypertension. However, initial optimism was overturned following the publication in 2014 of the results of the SYMPLICITY HTN-3 trial, again in TRH, in which the US Food and Drug Administration mandated a sham control. Here, in marked contrast to the earlier studies, there was no difference in BP between those who received RDN and those who underwent a sham procedure.

Subsequently, failure of a technique in SYMPLICITY HTN-3 that was so impressive in uncontrolled studies was attributed to regression to the mean, and the possibility that RDN may be both a powerful placebo and induce some patients to start to take their tablets more reliably. The failure led the Joint UK Societies (JUKS) to call for a moratorium on the use of RDN in routine clinical practice in the same year as the SYMPLICITY HTN-3 paper was published. It also led to recommendations for improvements to future studies, including careful patient selection, more complete delivery of RDN, using expert centres with experience in the techniques and better assurance of stable antihypertensive therapy throughout the studies.

Since the consensus statement of 2014, a number of second-generation studies have been reported. Of these, three studies (SPYRAL HTN-OFF MED, SPYRAL HTN-ON MED and RADIANCE SOLO) meet the new, more robust, study design proposed by JUKS, and have led to a reappraisal of the evidence for RDN in 2019: now published in Heart. SPYRAL HTN-OFF MED was a proof-of-concept study in patients with mild-to-moderate hypertension. In total, 80 patients not taking antihypertensive medications were randomised to RDN (n=38) or sham control (n=42). At 3 months, there was a significant reduction in both 24 hours systolic and diastolic ambulatory BP in the RDN group when compared with sham (−5.3 and −4.8 mm Hg, respectively). The SPYRAL HTN-ON MED had a similar design to SPYRAL HTN-OFF MED, the only major difference being that patients were taking one to three antihypertensive medications. It has reported on its first planned interim analysis following the randomisation of the first 80 patients assigned to either RDN (n=38) or sham (n=42). It showed a significant reduction in both systolic and diastolic 24 hours ambulatory BP at 6 months in the RDN group when compared with sham (−7.0 and −4.3 mm Hg, respectively).

RADIANCE SOLO study used a novel approach to RDN. Unlike the SIMPLICITY or SPYRAL studies, which used radiofrequency ablation, this study used ultrasound ablation of the renal sympathetic nerves. The study had a similar design to SPYRAL HTN-OFF MED, in that 146 patients with mild-to-moderate hypertension, not on antihypertensive medication, were randomly assigned to RDN (n=74) or sham control (n=72). At 2 months follow-up, there was a greater reduction in systolic daytime ambulatory BP in the RDN group with a baseline-adjusted difference between groups of −6.3 mm Hg. No significant adverse events were reported in these short-term studies.

These studies provide the strongest evidence to date that RDN leads to a sustained drop in BP at least in the short term with a reduction in systolic ambulatory BP of −6 mm Hg at 6 months. The design of these studies makes it hard to set them in the context of clinical care, but the effect on BP was modest at best and certainly no longer offering any sort of ‘cure’ for hypertension. Given the low cost and good tolerability of current treatments, one could argue that the focus of RDN should remain on TRH. However, when set against the results of the PATHWAY-2 study in TRH10 on home BP, the effects were similar to those of alpha-blockade with doxazosin and beta-blockade with bisoprolol, rather than that of the overwhelmingly most effective agent, the mineralocorticoid receptor antagonist spironolactone.

The JUKS consensus statement from key UK societies involved in RND—including experts in cardiology, hypertension, nephrology and radiology—is to be welcomed, as an up-to-date summary of the state of the art in RDN and, importantly, sets research priorities. The view, however, remains consistent—that RDN should only be offered to patients in the context of clinical trials. The evidence for RDN remains limited by small sample size, short duration and limited follow-up.

Significant questions remain about how effective RDN is in the long term, whether it may have harms that outweigh its benefits and how to identify those who will respond well to RDN. Until these questions can be answered, RDN will remain on trial.

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