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Renal denervation: An uncertain future

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It is now more than 5 years since I wrote my first commentary on renal denervation (RDN).[1] At the time, I was prompted by the contrast between the enormous enthusiasm for the technique, inspired by dramatic claims of >30 mmHg reductions in systolic blood pressure (SBP) observed in patients with resistant hypertension who had undergone RDN,[2–4] and the minimal falls in blood pressure (BP) when RDN was studied in well-controlled trials, particularly those involving sham-control procedures.[5–7] National bodies and international guidelines followed,[8,9] which recommended a moratorium on the widespread clinical uptake of RDN until such time as the true benefits or otherwise of RDN had been evaluated in well-controlled studies, in a variety of patient subgroups with hypertension and possibly other cardiovascular conditions, including heart failure.

Two important studies now deserve further commentary. SPYRAL HTN-ON MED[10] was a proof-of-concept randomised trial of BP lowering with the Symplicity Spyral multielectrode renal denervation catheter and the Symplicity G3 renal denervation RF generator (Medtronic), used to provide circumferential radiofrequency ablation treatments in a spiral pattern in the four quadrants of the renal artery and branch vessels. The control group received a sham procedure. A total of 467 patients were recruited into this trial, and subsequently 80 with uncontrolled BP (office SBP 150–180 mmHg, a 24-hour ambulatory SBP between 140 and 170 mmHg) and receiving one to three antihypertensive drugs were randomised to RDN or sham procedure. The primary efficacy end point was change from baseline ambulatory BP at 6 months. After 6 months, baseline-adjusted treatment differences between the RDN and sham control groups were −7.0/−4.3 mmHg for 24-hour ambulatory BP and −6.6/−4.2 mmHg for office BP in favour of RDN. Both results were statistically significant. No procedural or other adverse events were reported.

In SPYRAL HTN-OFF MED,[11] 331 patients with an office SBP between 150 and 180 mmHg were randomly assigned RDN using the same procedure as for the on-treatment trial or sham control. The primary efficacy end point was baseline-adjusted change in 24-hour SBP at 3 months. The treatment differences between the two groups at 3 months in favour of RDN were 3.9 mmHg for 24-hour SBP and 6.5 mmHg for office SBP. Both differences were statistically significant. Again, no procedural or other adverse events were reported.

Thus, after more than a decade, RDN comes of age. The sponsors of these trials are to be commended for mounting two well-designed and appropriately controlled investigations. Along with Symplicity HTN 3,[7] we now have a clear idea of the efficacy of this procedure in several subgroups of patients with hypertension. As I predicted in my earlier commentary, following the hype of the early unrealistic claims of substantial reductions in BP with RDN, we are seeing in most hypertensive patients that the procedure lowers 24-hour ambulatory SBP on average by about 5–7 mmHg and office SBP in some studies a little more. There is, like any intervention to lower BP, a considerable range in individual patient response, which is best explained by the marked heterogeneity of hypertension accounted for by the multiplicity of pathophysiological mechanisms involved in BP elevation in individual patients. In accordance with drug responses, with few exceptions such as age, race and renin status, there is no way that an individual response can be predicted. In earlier trials of RDN, catheter type, positioning and number of ablations might have accounted for some variation in response. Operator experience is also likely to have been an issue. Nevertheless, these recent studies now provide a clear picture of the overall effectiveness of RDN, and we now have to decide what role, if any, the procedure has in future practice. To put the BP lowering following RDN into perspective, the magnitude of the fall in SBP is equivalent to that following individual lifestyle measures and might be expected with a few kilograms of weight loss, regular physical exercise, salt restriction or reduction in alcohol intake.[12] Combinations of lifestyle measures would be expected to produce additive effects on BP lowering. Placebo-controlled trials of drug monotherapy in hypertension result, on average, in about 10 mmHg reductions in SBP.[13] Thus, RDN is about half as

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effective as a single drug and far less effective than two antihypertensive drugs in combination.[13] So, where do we envisage RDN fits in today's strategies for the treatment of the hypertensive patient?

In Symplicity-3,[7] a sham-controlled trial in patients with resistant hypertension, non-significant reductions in ambulatory SBP of 1.96 mmHg and office SBP of 2.39 mmHg were reported in favour of RDN.

I have argued that in resistant hypertension, the main problem is patient adherence with therapy.[14] In our most recent survey of more than 100 patients presenting with resistant hypertension, two thirds of the patients normalised their BP when drugs were administered under supervision and observed swallowing their tablets.[14] Many such patients would have been recruited into early uncontrolled trials of RDN. Some patients have undiagnosed factors contributing to apparent treatment-resistant hypertension, including obstructive sleep apnoea, excessive alcohol intake and other causes of secondary hypertension. Once these have been eliminated, a small proportion of patients are truly drug resistant. In this minority of patients, studies have shown that the addition of spironolactone in appropriate doses is highly effective[15] and at least as effective as RDN.[16]

Another group of patients who theoretically might benefit from RDN are those who seem to be intolerant of all medications. Such patients are a complex group of individuals who complain of adverse reactions to whatever antihypertensive drug is prescribed (and often to other classes of drugs). Many of these apparent adverse reactions are unrelated to the pharmacology of the drug and are best explained by the nocebo effect[17] – a real phenomenon and very difficult to manage. I remain uncertain as to whether an expensive invasive intervention is the appropriate way to manage such patients.

RDN has taught us a lot about the physiology of the circulation – the role of afferent and efferent renal nerves and their influence on other metabolic and hormonal systems.[18] However, its future place in the management of hypertension is, I maintain, very restricted, and future guidelines will clarify its role.

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