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SCIENTIFIC EDITORIAL

Renal denervation in hypertension: Towards a true revival?

Vers de nouveaux horizons pour la dénervation des artères rénales ?

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Background

Arterial hypertension is usually triggered by a complex interplay between numerous regulatory systems. In particular, an increased sympathetic tone is known to increase blood pressure (BP). Beta-blockers, alpha-blockers and centrally-acting drugs can modulate sympathetic activity, but their effectiveness in controlling BP is usually insufficient and limited by side-effects [1]. Over the past decade, device-based therapies, including endovascular catheter-based renal denervation (RDN) and carotid baroreceptor stimulation, have been proposed to target the autonomic nervous system, and are still being evaluated. RDN aims to partially destroy renal afferent and efferent sympathetic nerves spreading around renal arteries, thereby reducing sympathetic efferent and afferent signalling to and from the kidneys [2].

Since 2010 and the early trials on RDN, many questions have been raised and addressed progressively. The most relevant issues include: identification of resistant hypertension as a particular entity; the true effect of RDN, and identification of potential good responders to the technique; and the major concern regarding adherence to

Abbreviations: BP, blood pressure; RDN, renal denervation.

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antihypertensive treatment. We will focus on the last two topics.

Does RDN lower BP?

In 2010, the first trial on RDN, using mainly a monopolar radiofrequency catheter (Symplicity™; Medtronic Inc., Minneapolis, MN, USA) in patients with severe hypertension, reported reductions of > 30 mmHg in office systolic BP [3,4]. These studies raised criticisms concerning the BP measurement (absence of ambulatory BP measurement), the confounding effect of concomitant antihypertensive treatments (no standardized treatment, absence of adherence assessment) and the open-label design (Hawthorne effect), which may have led to overestimation of results [5,6]. Because of these potential biases, the Symplicity HTN-3 study, a large randomized sham-controlled trial (renal angiography alone), with both office and ambulatory BP measurements, was conducted in the USA. This study, published in 2014, reported no significant office or ambulatory BP-lowering effect of RDN, although the safety endpoint was met [7]. However, despite its improved design, involving a sham procedure, this trial had various drawbacks that limited the robustness of its conclusions, including:

- uncontrolled changes to antihypertensive treatment during the trial;
- insufficient operator skill, leading to incomplete RDN;
- lack of treatment adherence assessment;
- inclusion of patients with isolated systolic hypertension [8].

Later, the French open-label randomized controlled DENERHTN study, conducted in the French Network of Hypertension Excellence Centres, demonstrated a significant reduction of 6 mmHg in daytime ambulatory systolic BP with RDN combined with a very rigorous standardized stepped-cared antihypertensive treatment versus the same standardized medical treatment alone [9]. The absence of a sham procedure in the control group was a limitation of this study; however, adherence to antihypertensive treatment was assessed by drug screening of urine/plasma samples [10]. These data confirmed that adherence to the antihypertensive treatment regimen of the trial was poor, even in the context of severe hypertension, with around 50% of patients being adherent. Interestingly, a significant reduction in BP was also observed in non-adherent patients, suggesting that this may be an appropriate setting in which to evaluate the BP-lowering efficacy of RDN. All of these studies were safe, reporting no increased incidence of serious adverse events, allowing the effects of RDN to be investigated with new trial designs using new catheters.

Indeed, all the initial trials on RDN raised various methodological concerns. Many aspects were discussed in an attempt to optimally design the next generation of randomized controlled clinical trials of autonomic modulation therapies targeting hypertension [11]. Requirements include blinding of patients with a sham group, which necessitates renal angiography alone under profound analgesia. Blinding of the physicians assessing BP outcome during follow-up is also mandatory, and requires them to be independent of the interventional team. Untreated patients with mild-to-moderate hypertension should be included, to avoid the confounding effect of unreliable treatment adherence. Alternatively, patients with resistant hypertension should be included, with the following criteria: more than three antihypertensive drugs in adequate dosage, including a diuretic; exclusion of secondary hypertension; use of ambulatory BP monitoring; preserved renal function (glomerular filtration rate > 45 mL/min/1.73 m^2); and eligible renal arteries.

Three new randomized sham-controlled trials with optimized designs have definitely demonstrated that RDN lowers ambulatory and office BP significantly, by a magnitude that is clinically pertinent.

Two international multicentre single-blind randomized sham-controlled trials (SPYRAL-OFF MED and RADIANCE-HTN SOLO) included patients with grade I–II primary hypertension while off antihypertensive medication, and were published in *The Lancet* [12,13]. Patients were randomized after a 4-week discontinuation of antihypertensive treatment on the basis of ambulatory BP measurement. Patients with grade III hypertension were excluded. The primary endpoint was to compare the change in 24-hour ambulatory systolic BP at 3 months with the Symplicity Spyral™ multielectrode radiofrequency catheter (Medtronic; SPYRAL-OFF MED) and the change in daytime ambulatory systolic BP at 2 months with the ultrasound-based Paradise® RDN system (ReCor Medical, Inc., Palo Alto, CA, USA; RADIANCE-HTN SOLO) versus a sham procedure restricted to renal angiography only. Renal artery anatomy was carefully selected to enable complete nerve ablation of both renal arteries with either catheter. SPYRAL-OFF MED was a small proof-of-concept study that included 80 patients, and was not powered for efficacy; in contrast, RADIANCE-HTN SOLO was powered for efficacy, and included 146 patients. More than 45 bilateral renal ablations in the main, polar and branch arteries were performed in SPYRAL-OFF MED, whereas 5.4 ablations restricted to the main renal arteries were performed in RADIANCE-HTN SOLO. Both studies reported a significant and clinically pertinent reduction in systolic ambulatory BP (of 5–6 mmHg) and systolic office BP (of 6–10 mmHg) in favour of RDN compared with the sham procedure. As previously reported, there was large between-patient variability in the BP response to RDN, which was also present in the sham-control group. No major adverse events occurred in either trial during the short follow-up periods. The magnitude of the BP reduction in these two trials was similar to that reported with first-line antihypertensive monotherapy (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, thiazide diuretics and calcium channel blockers) [14].

The third randomized single-blind sham-control proof-of-concept trial, including 80 patients with uncontrolled hypertension despite treatment with one or two antihypertensive medications, also showed a significant reduction in 24-hour systolic ambulatory BP of 7 mmHg in favour of RDN with the Symplicity Spyral™ catheter compared with the sham procedure at 6-month follow-up [15]. Again, the short-term safety profile of the intervention was favourable, with no major adverse events recorded. These results will hopefully be confirmed by another well-designed trial using ultrasound ablation (RADIANCE-HTN TRIO) [16].

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