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What we need to know about renal nerve ablation for treatment of hypertension and other states of sympathetic overactivity

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Introduction

Renal nerves play a crucial role in regulation of kidney function and blood pressure (BP) control. Compelling evidence exists from both animal and human studies to demonstrate that activation of renal sympathetic nerves play a critical role in the pathogenesis of hypertension. Denervation of the kidneys achieved predominantly by surgical stripping and/or chemically was primarily applied in experimental settings as a means to investigate the physiological role of renal nerves. Clinically, the concept of targeting sympathetic nerves including those innervating the kidneys culminated in the relatively widespread use of surgical splanchnicectomy for treatment of severe hypertension in the early 20th century. Plagued by frequent and sometimes debilitating adverse consequences and with the advent of effective pharmacologic treatment options surgical sympathectomy was soon abandoned. Advances in biomedical engineering allowed a more specific and direct approach to target renal sympathetic nerves (17) and randomized clinical studies (10) sparked substantial interest in the scientific and medical community and led to expedited introduction into clinical medicine in several countries. A subsequent larger and more rigorously designed randomized clinical trial while confirming the safety of the procedure failed to demonstrate efficacy compared to a sham procedure (4). Clinical trial design, endpoints and their evaluation, patient selection and management both before and after renal denervation and predictors of the BP response are just some of the aspects that have been scrutinized in the aftermath of Symplicity HTN-3 and remain to be addressed in ongoing or planned clinical studies (11, 28). Equally important though, is a better understanding of the structural and functional consequences of various treatment modalities and their effects on renal, vascular and neuronal aspects of kidney function and BP control (11, 28-29). Sophisticated experimental studies in relevant animal models are warranted to address these issues and may help to render therapeutic renal denervation approaches more effective.

The role of renal nerves in BP control

A large body of experimental work (7) and several studies in humans (12, 30-31) have demonstrated that chronic activation of renal sympathetic nerves is a crucial contributor to the pathogenesis and perpetuation of elevated BP. Similarly, renal sympathetic nerve activation is a common feature in conditions frequently occurring as a consequence of sustained hypertension such as chronic kidney disease (32) and heart failure (33). In fact, renal noradrenaline spillover

predicts outcomes in heart failure patients (23). As recently summarized in an elegant review, renal sympathetic nerves are necessary in the pathogenesis of congestive heart failure both via efferent and afferent mechanism (27). The mechanisms through which sustained efferent sympathetic outflow to the kidneys elevates BP include alterations in renal vascular resistance (16), release of renin from juxtaglomerular granular cells (36) and increased tubular sodium and water reabsorption (3). Excitatory reflexes originating from afferent renal nerves in the kidney contribute further and are triggered by renal ischemia, injury or elevated adenosine concentrations (32).

Translation of renal physiology: Clinical Trial data on renal denervation

Based on these physiological principles and faced with the need for alternative therapeutic approaches to curb the burden of hypertension, specifically resistant hypertension, the development of catheter-based techniques using radiofrequency energy to ablate the renal nerves ensued and was tested initially in the Symplicity HTN-1 and HTN-2 trials (17,10) demonstrating the feasibility and short-term safety of the approach with office BP lowering effects of 25-30 mmHg which were sustained up to at least 36 months (18,9).

However, Symplicity HTN-3 the largest and first randomised, double-blinded, sham-controlled trial (4) including a total of 535 patients with resistant hypertension assigned in a 2:1 ratio to receive either the RDN or sham-procedure failed to demonstrate a significant difference in BP reduction between the two treatment groups (RDN: -14.1/6.8 mmHg vs Sham: -11.7/4.8 mmHg; P=0.26). Concomitantly, no superior treatment effect of RDN over the sham-procedure for mean change in 24-hour (p=0.98), daytime (p=0.52) or night-time (p=0.06) ambulatory SBP was observed (2). A number caveats with the Symplicity HTN-3 study design have since been identified that are likely to have contributed to the neutral findings. Specifically, despite the inclusion of a sham-procedure, the majority of interventional cardiologists were inexperienced in performing the procedure, bilateral circumferential ablation was only achieved in 6% of patients with RF energy preferentially applied to the proximal portion of the renal artery. Furthermore, no assessment of renal denervation efficacy was obtained and patient's medication regime prior to testing at baseline and 6-months was not stable (11, 28, 22).

More recently, several prospective, randomised controlled trials have reported either a modest or no effect of RDN on BP reduction in patients with resistant hypertension, each with their own limitations (13, 1, 6, 25). Two of the studies showed RDN to be at least equally effective (13, 25) to intensive pharmacotherapy in lowering BP in patients with true resistant hypertension, highlighting the ability of RDN to lower BP at least to the extent of additional pharmacologic treatment. The DENERV-HTN (1) study compared RDN in combination with standardised, stepped-care antihypertensive treatment (SSAHT) and observed a modest, albeit significant reduction in 6-month daytime SBP (adjusted mean difference of -5.9 mmHg (95% CI: -11.3, -0.5; p=0.03) compared to SSAHT alone (1). Another study (6) applying a sham controlled study design not dissimilar to that used in Symplicity HTN-3 found that in the per-protocol analysis, those who underwent RDN experienced a significantly more pronounced reduction in mean 24-hour and daytime systolic BP at 6-months follow-up compared to patients treated with a sham-procedure (-8.3 ± 8.9 mmHg vs. -3.5 ± 9.5 mmHg; p=0.04).

Critical issues to be addressed in experimental studies

In depth knowledge of renal nerve physiology obtained primarily from sophisticated experimental studies laid the foundations for the exciting development of catheter-based renal denervation as a promising clinical application. Once more, and in close collaboration with clinical scientists, we will rely on the scientific community of physiologists and experimentalists to lead the field further and gain more insights to improve and optimise our therapeutic efforts.

While there is good evidence to demonstrate that surgical RDN can prevent or delay the onset of hypertension in various experimental models (8), the efficacy and safety of catheter-based transluminal approaches are less well investigated. Important initial data from a swine model (24) demonstrated that treatment with a single electrode RF catheter resulted in fibrosis of the media and adventitia ranging from 10 to 25%. Mild disruption of the external lamina elastica was seen but no intimal lesions or thrombosis was evident 6 months after the procedure. Aside from fibrosis renal nerve injury involved replacement of nerve fascicles with fibrous connective tissue, and thickening of the epineurium and perineurium (24).

The relevance of a deeper understanding of lesion formation and its consequences with radiofrequency energy or other types of energy became apparent after Symplicity HTN-3 was

published and insufficient denervation efficacy was identified as possible explanation for the neutral findings. Consequently, research efforts focussed on several relevant aspects including the biophysics of radiofrequency induced lesion formation (21), the anatomical distribution of the nerve plexus around the renal arteries (34), and the density of peri-arterial renal sympathetic nerve fibers in relation to the proximity to the aorta (35). These important findings and their translation facilitated optimization of the therapeutic approaches as exemplified by the demonstration of more pronounced reductions in renal noradrenaline content with RDN being preferentially performed in distal segments of the main renal arteries and in renal artery branches compared to preferential proximal ablation (14,19). Open questions remain in regard to the ideal treatment approach, the required and ideal depth of lesions, the role of renal nerves not travelling along the renal arteries, the safety and efficacy of circumferential single plain denervation approaches as can be achieved with ultrasound both in the main artery but also in branches and many more.

Longer-term consequences of renal denervation for renal artery and nerve anatomy, as well as the capacity of the renal nerves to regrow also require further investigation. Sakakura and colleagues (16) studied the time course of nerve and vascular damage following RDN achieved by single electrode radiofrequency ablation in swine at 7, 30, 60 and 180 days after RDN and demonstrated that renal arterial injury decreased progressively and resulted in complete healing of the arterial wall at 6 months post procedure. However, focal nerve regeneration was observed at the sites of radiofrequency delivery, both at 60 and 180 days (16). These data clearly support the notion that anatomical re-innervation is possible after a radiofrequency insult but do not answer the question of the functional relevance of the regenerated nerve fibres. Single electrode catheter-based RDN applied in a normotensive sheep model also demonstrated re-innervation around 11 months after the RDN procedure as indicated by restored responses to electric nerve stimulation of the renal efferent nerves (5). The integrity and functionality of afferent renal nerves, presumed to play a relevant role in BP responses to RDN (32, 33) before and after radiofrequency ablation or other RDN modalities is an important unanswered question that remains to be investigated.

Despite many open questions it is reassuring that data is now available from both small (rats) (19) and large (dogs) (15) animal models of hypertension, the latter closely mimicking cardiorenal and metabolic changes in obese hypertensive humans, to demonstrate the efficacy of catheter-based renal denervation approaches to lower blood pressure significantly.

Clinical progress in this area will depend to a large extent on high quality experimental studies in relevant models of disease to investigate the many open questions touched upon above. To put it simply, the main issue to be addressed in the absence of a BP response to renal denervation is whether this is due to a technical, i.e. insufficient denervation, or a pathophysiologic failure, i.e. renal sympathetic nerve activity not being a major driver of the elevated BP level. Additional aspect that require our attention include more accurate determination of the relevance of efferent vs afferent nerve activity, the short and long-term effects of catheter-based RDN on both, details in regards to the safety of treating smaller and even intra-parenchymal renal artery branches, the exact mechanisms by which RDN confers sustained BP lowering, identification of biomarkers to predict BP responses to RDN and to monitor technical success, and more.

The journey has merely begun....

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