Editorial

Denervated or Not? That Remains the Question for Renal Denervation

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Since its inception a decade ago,[1] the renal denervation procedure to treat high blood pressure has been impeded by the problems of patient selection and an unequivocal readout of procedural efficacy. Historically, this has been the Achilles heel of the technique that was so drastically emphasized by the recent Symplicity Hypertension-3 trial[2] concluding no difference in the blood pressure response between operated and sham groups. However, in this issue of *Hypertension*, Liu et al[3] gives much-needed encouragement and novel insight to the old problem.

The multifactorial nature of high blood pressure makes it futile to believe that any single intervention will neither normalize blood pressure nor reduce it in all patients. It is reasonable to propose, however, that renal denervation will lower blood pressure in a significant proportion of patients with hypertension. From real world studies the consensus is around 50%, with very few patients hitting target pressure levels).[4] The magnitude of the fall in arterial blood pressure will likely depend on the severity of the hypertension, the presence and type of medications being taken by the patient, the completeness of the denervation and if the driving mechanisms causing high blood pressure include activity within the renal nerves.

It should not be surprising that denervating the renal nerves causes blood pressure to fall as it targets multiple mechanisms that cause blood pressure to rise. These include sympathetically mediated reduction in (1) renin release and subsequent attenuation of angiotensin and aldosterone activity, (2) sodium reabsorption, and (3) renal artery vasoconstriction. In addition, there will be abolition of reflexly mediated rises in arterial pressure mediated by sensory nerves if they are tonically active. Given that these afferent fibers are heterogeneous in function mediating increases and decreases in blood pressure, one has to hope that the net effect is that the pressor afferents exert a greater influence than the depressor sensory fibers. But, despite extensive correlations and regression analyses, robust identification of patient responders to renal denervation is lacking.

So, what about procedural efficacy. Classically, pharmacological treatment must demonstrate engagement of the target by the drug. This can be demonstrated, for example, by the absence of a response to an agonist in the presence of the therapeutic antagonist or vice versa. By analogy, an interventional approach should be challenged to ensure the treatment has been effective. Unfortunately, to date, no efficacy challenges are known for renal denervation, and this promotes performing high numbers of ablations along the renal artery, which may be wholly unnecessary and increase the risk of damaging the artery and prolong procedure time.

Published in *Hypertension*, Liu et al[3] report on a method to accurately guide procedural efficacy. The special appeal with this study is that it may also be used to guide patient selection for renal denervation. Thus, this study may finally address the Achilles heel of renal denervation. The study used a hypertensive canine model and compared the blood pressure fall obtained after renal denervation with ablations at predetermined sites along the renal artery that gave either small or large increases in blood pressure during transmural electrical stimulation. The study indicates that ablation at sites giving larger pressor responses was predictive of a greater antihypertensive response than at sites in which smaller pressor responses (or depressor responses) were evoked. The authors showed that the sites from which large pressor responses were evoked, and bigger antihypertensive responses produced, contained higher densities of nerves. The nerves identified were autonomic (sympathetic and parasympathetic) as well as sensory afferents but it remains to be determined which nerve types were responsible for the transmurally evoked pressor responses on stimulation. They could include afferents and sympathetic nerves. However, given the close spatial proximity of efferent and afferent nerves (often found intertwining) it is unlikely that ablation at a pressor site contains purely one nerve fiber type. This study in dogs fully compliments and supports the data from small trials in humans, which concluded that renal nerve stimulation should be tested to assess the efficacy of renal denervation and predictor of the blood pressure lowering response.[5] Given this, there is every reason to believe that the canine data are transferable to humans.

On the basis of these potential landmark findings, the question posed is whether we can stimulate the renal nerves noninvasively as a method to first screen patients. Practically,

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this means we need a system that allows precise activation of nerves/nerve plexus on the renal artery. Is this possible? Focused ultrasound may be one such approach, and this has been trailed recently in vivo to functionally activate the sciatic nerve in mice.[6] The advantage is the ability to orientate and focus the energy at deep structures. Additionally, renal denervation catheters should also accommodate the ability to stimulate nerves transmurally and not only ablate. Given that many renal nerves may not run either within or on the renal artery, stimulation devices offering the ability to focus energy beyond the artery in a circumferential manner may be best suited to both stimulate and ablate renal nerves.

In conclusion, the current article by Liu et al[3] gives hope that the hype of Symplicity Hypertension-1 ten years ago[1] might finally rebound in a reflective wave of triumph and deliverance of a much needed new frontline procedure for the treatment of hypertension that permits a high degree of patient selectivity and demonstrable procedural efficacy.

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