In this issue, Booth et al.¹ use a unique combination of functional, anatomical, and biochemical techniques to determine the effectiveness of percutaneous catheter-based radiofrequency renal denervation (RDN) on the destruction of the renal nerves and the long-term pattern of functional reinnervation. Their work is timely given the failure of the only appropriately powered, blinded, sham-controlled RDN clinical study to meet its primary end points,²,³ and indeed the future of the technique powered, blinded, sham-controlled RDN clinical study to meet its primary end points,²,³ and indeed the future of the technique is now being questioned.⁴,⁵ Although issues of procedural competency and suboptimal denervation have been raised,⁶ it is now more important than ever for the basic mechanisms underlying RDN to be clarified because specific patient cohorts may still show better responsiveness to therapy,⁵ and secondary benefits of RDN in conditions such as diabetes mellitus, chronic kidney disease, and heart failure are still under investigation.⁴ Whether primary beneficial effects are because of removal of afferent (sensory), efferent (sympathetic), or both components of the renal nerve also remains to be elucidated. One of the more puzzling issues associated with the procedure is the reported time frame of effectiveness, with data from the Symplicity HTN-1 and HTN-2 studies suggesting long-term changes in blood pressure in patients with treatment-resistant hypertension out to 36 months post RDN.⁷,⁸ This is despite strong evidence in small animal models that reinnervation of both the sensory and the sympathetic renal nerves occurs over a relatively rapid time course (2–4 months) with functional capacity.⁹–¹¹ A limitation in translating work from small animal models to human clinical treatments is the methodology used to achieve denervation, which in the experimental situation typically involves the use of full surgical exposure of the renal nerves, stripping of the renal nerves, and the application of a 10% solution of phenol.⁹ Such an approach achieves full denervation when compared with catheter-based RDN, which in controlled studies in humans has been shown to achieve a mean efficacy of 47%, as determined by renal noradrenaline spillover methods.⁶

Booth et al.¹ tackle these questions head on, using a large animal ovine model to examine not only the immediate impact of RDN on both the renal afferent and the efferent nerves but also the degree of reinnervation at 5.5 and 11 months post RDN. In the first instance, they demonstrate that 1 week after RDN using the Symplicity RDN System, renal sympathetic and afferent nerve functions in the sheep are abolished. Critically, they then show in further cohorts of animals that at 11 months post denervation, both levels of renal sympathetic nerve activity, as determined by direct recording, and physiological responses to sympathetic and sensory renal nerve electric stimulation, have returned to normal levels. This was supported by immunohistochemical assessment of the anatomic distribution of afferent and efferent nerves within the kidney and renal noradrenaline levels using high-performance liquid chromatography. The authors then correctly state that their findings challenge the notion that a long-term effect of RDN on renal afferent or efferent nerve function underlies the sustained reduction in blood pressure responses that have been documented in hypertensive patients.¹

The methodology used by Booth et al.¹ deserves a comment with regard to their approach to provide specific information about functional reinnervation by both arms of the renal nerve. By determining the cardiovascular and renal blood flow responses to proximal and distal stimulation of the renal nerve in control animals, as measures of afferent and efferent functions, respectively, their measurements of the same parameters after stimulation of the whole renal nerve in RDN animals allowed them (i) to gauge the degree of the initial denervation effectively, which is critical from both research and clinical perspectives, and (ii) to assess the long-term functional reinnervation of both the sensory and the sympathetic renal nerves. When supplemented with their anatomical and biochemical studies, it provides overall convincing evidence that significant reinnervation occurs after catheter-based RDN within a 12-month time frame.

A limitation of the study, particularly for the acute experiments determining the immediate impact of the denervation procedure, is the lack of a sham group. In animal models, the sham RDN procedure has been shown to have an effect,¹² and while a placebo effect or increased adherence to antihypertensive treatment¹³ is not of direct relevance, the impact of the sham surgery should be determined in a comparably succinct and thorough fashion as undertaken in the current study. It should also be noted that the study was performed in young, healthy normotensive animals, and as the authors correctly identify, it remains to be determined whether age or concurrent disease status influences the rate or functionality of nerve regrowth.

In view of the evidence provided in the work of Booth et al.¹ what then underlies the prolonged hypotensive effect of catheter-based RDN in humans?⁷,⁸ The authors consider the impact of RDN on renal blood flow, sodium reabsorption, the renin angiotensin system, and the renal sensory afferent reflex (renorenal
reflex) as potential alternative mediating mechanisms. Another potential mechanism for consideration is that even a limited period of reduced renal afferent input to the central nervous system may result in long-term changes to additional homeostatic reflex pathways that otherwise contribute to the hypertensive state. Short-term studies in rodents and humans for example indicate that cardiac and sympathetic baroreflex functions improve after RDN, even when no change in blood pressure was achieved. In conclusion, the work of Booth et al provides a critical step forward in our understanding of the chronic effects of RDN, applying the same device as used in human clinical trials to a large animal model, and carefully documenting anatomical and functional evidence for successful initial denervation, and both renal afferent and efferent reinnervation over an 11-month time frame. Although this work suggests that correct and careful adherence to the RDN procedure can ensure a successful denervation, it does not lend support to long-term denervation being the mechanism underlying sustained effects, and this is where future research efforts must now be directed.

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What Underlies the Prolonged Hypotensive Effect of Catheter-Based Renal Denervation in Humans?

Jacqueline Kathleen Phillips

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