

# Microanatomy of the Renal Sympathetic Nervous System

The anatomic substrate for renal denervation.

BY FARRELL O. MENDELSON, MD

A hyperactive sympathetic nervous system is a key driver of hypertension. This system can be thought of as a loop of electrical activity with the kidney at the center of the circuit. Electrical signals travel from the brain, down the spinal cord, and then to and from the kidney in the renal sympathetic nerves, returning up the spinal cord to the brain. This circuit increases sympathetic outflow to the entire cardiovascular system.<sup>1</sup> Electrical stimulation of the kidney via the efferent renal nerves leads to vasoconstriction of the renal vasculature, increased release of renin, and tubular reabsorption of sodium. Signaling back from the kidney via afferent renal nerves increases total peripheral vascular resistance. The net effect of this entire cascade of events is a rise in blood pressure.

The renal sympathetic nervous system was a therapeutic target for antihypertensive treatment decades ago, when surgical sympathectomy was the only option for patients with blood pressure that was difficult to control.<sup>2</sup> Although effective, surgical targeting of renal sympathetic nerves lacked precision and resulted in collateral nerve damage, which led to orthostasis, bowel and bladder incontinence, and sexual dysfunction. Not surprisingly, this technique was abandoned with the advent of effective pharmacologic antihypertensive therapy.

## RENAL DENERVATION MECHANISMS

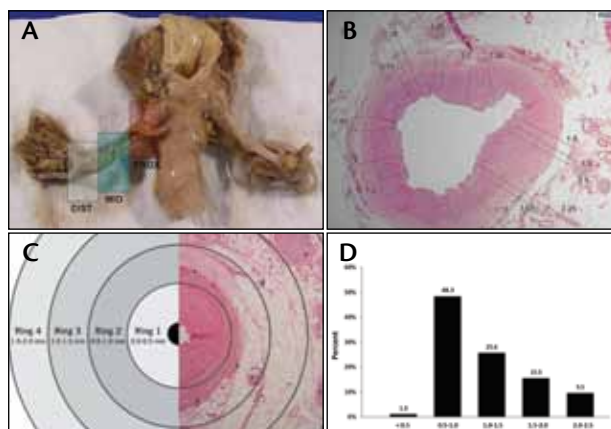
Despite the plethora of drugs used for treating hypertension, millions of patients worldwide continue to experience

high blood pressure.<sup>3</sup> The publication of data from the Symplicity HTN-1 trial in 2009 was a watershed event for patients with resistant hypertension.<sup>4</sup> The trial reported on the first experience using the Symplicity renal denervation system (Medtronic, Inc., Minneapolis, MN). This system is composed of a single-electrode radiofrequency ablation catheter connected to an automated generator. The catheter is placed into the renal artery with the tip apposed to the vessel wall, and the generator delivers up to 8 watts of power via the catheter into the tissue for 2 minutes at a time. Since the publication of Symplicity HTN-1, a variety of renal denervation systems have been developed, which use either energy (radiofrequency or ultrasound) or chemical methods to interrupt the renal sympathetic nervous system.

The energy delivery systems cause heating of the renal artery wall to temperatures exceeding 50°C and result in irreversible tissue damage. While endothelium (to a small degree), smooth muscle, and fibrofatty connective tissue are injured in this process, the renal sympathetic nerves running along the artery wall constitute the anatomic target of all denervation systems.

## OUR STUDY

We reported the first human microanatomic study of renal sympathetic nerve distribution in 2012.<sup>5</sup> Nine renal arteries free of atherosclerotic plaque were harvested from five human autopsies and were longitudinally sec-



**Figure 1.** A human postmortem specimen of renal artery with boxes indicating proximal, middle, and distal artery segments (A). A hematoxylin- and eosin-stained histologic cross-section of the renal artery with lines indicating the distance from the lumen-intima interface to the renal nerve (B). A polar map identifying renal nerves in 0.5-mm-deep rings extending out from the renal artery lumen (C). A bar graph depicting the frequency of nerves within each 0.5-mm ring out to 2.5 mm from the renal artery lumen (D). Panel (C) is reproduced and (D) is modified with permission from Atherton DS, et al. *Clin Anat.* 2012;25:628–633.<sup>5</sup>

tioned into three parts (proximal, middle, and distal to the ostium) (Figure 1A). Each section was prepared for microscopy with hematoxylin and eosin staining to visualize the renal nerves, and nerve numbers were manually counted.

We found that the nerves were circumferentially distributed around the renal artery and not clustered in any way. There is a myth that the renal sympathetic nerves increase in number near the ostium of the artery, and thus renal denervation ablations must be performed in this location. Our findings refute this theory: the number of nerves increased along the length of the artery, with a total of 216 in the proximal section, 323 in the middle section, and 417 in the distal section. The increasing nerve counts along the length of the artery likely reflect an arborization pattern of the nerves. This longitudinal distribution of nerves has varied somewhat in other reports.<sup>6,7</sup> Regardless, denervation at any point along the renal artery should interrupt the electrical signal in the efferent and afferent nerves within the target region.

We also measured radial distances from the lumen-intima interface to each nerve with a micrometer (Figure 1B). For the purposes of our analysis, the nerves were grouped into 0.5-mm-deep rings, emanating out from the lumen like a topographic map (Figure 1C). We

found that 90.5% of all renal sympathetic nerves reside within 2 mm of the renal artery lumen (Figure 1D).

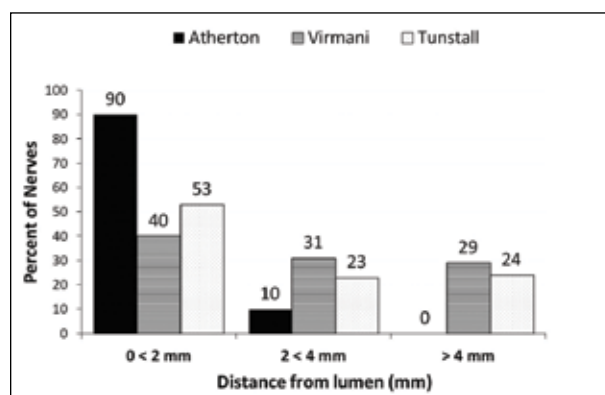
## DISCUSSION

As follow-up to our study, Tunstall et al<sup>8</sup> and Virmani<sup>6</sup> have each reported similar analyses of human renal sympathetic nerve depth. Their studies differed from ours by (1) including specimens with atherosclerotic plaque and (2) taking deeper cross-sections of the renal artery. Renal sympathetic denervation, as currently practiced, is not performed in renal arteries with significant plaque; arteries with plaque were therefore excluded from our analysis in order to mimic the clinical situation.<sup>5</sup> Measuring nerve depth in arteries with plaque will unquestionably increase the depth measurement compared to specimens without disease.<sup>8</sup>

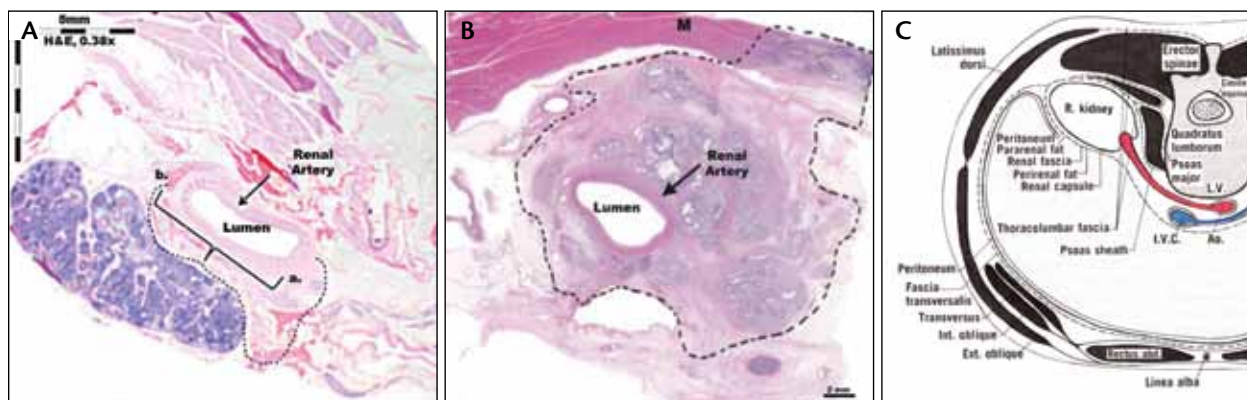
In their respective studies, Tunstall et al<sup>8</sup> and Virmani<sup>6</sup> captured some renal nerves that were deeper than in our report (Figure 2). This discrepancy may partially be explained by their inclusion of arteries with plaque. Some sections contained nerves that were 8 mm or more from the renal artery lumen, but it is unclear whether these nerves actually travel to the kidney or innervate other organs.

In hypertensive patients, the renal nerves may actually be closer to the lumen<sup>7</sup> and thus more susceptible to renal denervation technologies. Furthermore, immunohistochemistry techniques have identified nerves, not apparent with routine hematoxylin and eosin staining, that are in very close proximity to the renal artery lumen.<sup>8,9</sup>

This issue of nerve depth is not simply one of academic interest. For clinical success, renal denervation techniques must effectively ablate the renal sympathetic nerves while at the same time avoiding injury to adjacent organs. The two swine case examples in Figures 3A



**Figure 2.** A bar graph comparing the distribution of renal nerve depth in reports from Atherton et al,<sup>5</sup> Virmani,<sup>6</sup> and Tunstall et al.<sup>8</sup>



**Figure 3.** A histologic cross-section of swine renal artery treated with a balloon-based denervation catheter with a helical array of ablation electrodes. The dotted line indicates the region of injury extending 3 to 4 mm deep into the renal artery wall (A). Image provided courtesy of Boston Scientific. © 2013 Boston Scientific Corporation or its affiliates. All rights reserved. A histologic cross-section of swine renal artery treated with alternative circumferential injury technology (B); the dotted line indicates the region of injury extending > 8 mm deep into the renal artery wall and beyond into the psoas muscle ("M"). An illustration of a human abdominal cross-section with the psoas muscle posterior to and peritoneal cavity anterior to the right renal artery (red area) (C). Adapted with permission from Rand S. Swenson, <http://www.dartmouth.edu/~humananatomy/index.html>.

and 3B illustrate this point. Figure 3A shows a histologic cross-section through a renal artery treated with a renal denervation balloon catheter mounted with a helical array of ablation electrodes. This temperature-controlled denervation system consistently produces an ablation lesion extending to a depth of 3 to 4 mm into the artery wall (Figure 3A). In an animal model of renal denervation efficacy, the renal nerve injury achieved with this device was comparable to open surgical stripping of renal nerves, thus confirming the effectiveness of an ablation strategy that targets nerves within 4 mm of the artery lumen. Figure 3B shows a similar histologic cross-section but with an alternative technology for circumferential renal nerve injury. The ablation depth with this device exceeds 8 mm and, in this specimen, resulted in injury of psoas muscle posterior to the artery. Figure 3C illustrates the close proximity of psoas muscle to the renal artery posteriorly. The peritoneal cavity with bowel resides just anterior to the renal artery and poses a dangerous clinical hazard when deep denervation techniques are employed.

## CONCLUSION

Despite the potential hazards, renal sympathetic denervation systems in current clinical use offer a safe and effective therapy to millions of patients worldwide who have hypertension that is difficult to control. The renal sympathetic nerves are the anatomic substrate for this promising new therapy, and their close proximity to the renal artery lumen makes them susceptible to various forms of transarterial injury. Knowledge of renal

nerve microanatomy is critical for practitioners of denervation to understand the mechanism of this procedure and is essential for the development of renal denervation technologies. ■

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*Farrell O. Mendelsohn, MD, is Director, Interventional Hypertension Therapies Program, Cardiology PC in Birmingham, Alabama. He has disclosed that he has received consulting fees from Boston Scientific Corporation, Vessix Vascular, Inc., and Medtronic, Inc. Dr. Mendelsohn may be reached at (205) 780-4330; [fmendelsohn@cardiologypc.com](mailto:fmendelsohn@cardiologypc.com).*

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