To the Editor:

We read with interest the article by Sakaoka et al., in Catheterization and Cardiovascular Interventions entitled, "Safety of catheter-based radiofrequency renal denervation on branch renal arteries in a porcine model.”

Renal sympathetic nerve activation is central in the pathogenesis of hypertension. In the 1940s, surgical denervation was found to reduce blood pressure (BP) in hypertensive patients and animals, but was fraught with a significant number of side effects. More recently, catheter-based devices for renal denervation (RDN) in the treatment of resistant hypertension have shown to be successful in the SPYRAL HTN-OFF MED and SPYRAL HTN-ON MED trials. One way in which these two trials differed from their preceding negative trial trial was that they included ablation of the renal artery (RA) branches in addition to the main RA. Additionally, a number of studies directly comparing RDN of the main RA versus the main RA and its branches have shown greater BP reduction with the latter technique. There is a risk of RA stenosis with RDN via a peri-arterial approach, which may be increased when ablating smaller branch RAs. We agree with the authors that RDN of branch RAs needs further investigation, and congratulate them on their study demonstrating the safety of radiofrequency RDN on branch renal arteries, specifically in that there was no histopathological evidence of artery stenosis or kidney injury after ablation.

In their study, Sakaoka et al. used the IberisBloom RDN system (Terumo Corporation, Tokyo, Japan) compared to the Symplicity Spyrail (Medtronic, Minneapolis, MN) used in the SPYRAL HTN-OFF MED and SPYRAL HTN-ON MED trials. Compared head-to-head, the two devices resulted in similar reductions in norepinephrine (NE) levels and histopathologic lesion characteristics. Just as important as demonstrating the safety of branch RA ablation, it is of interest to know the nerve fiber-type (afferent vs. efferent), distribution, and depth of the nerves in the renal branch arteries.

We believe a better understanding of the underlying renal anatomy and physiology would be beneficial in the application of RDN technology. For example, the kidneys are innervated by both efferent and afferent nerve fibers. Denervation of either nerve fiber can theoretically decrease BP: Ablation of afferent renal nerves can decrease BP by decreasing the sympathetic drive to the kidney and other organs; ablation of efferent renal nerves can reduce BP by decreasing renal vascular resistance, renin release, and sodium and water reabsorption. Recent studies however suggest it is ablation of afferent nerves that is the putative factor in the antihypertensive effects of RDN. The study by Sakaoka et al. used a reduction in NE as a surrogate for effective RDN, which is a common methodology in other studies as well. Unfortunately, a decrease in NE is not indicative of afferent nerve ablation. NE reduction is a measure of efferent activity; there is no good marker or measure for afferent activity. Since afferent and efferent nerves are intertwined within the kidney, by showing a disruption in efferent activity (NE reduction) there is a presumption that afferent activity is also being affected. The afferent renal sensory nerves contain substance P and calcitonin gene-related peptide (CGRP) as its primary sensory neurotransmitters. Similarly, efferent renal sensory nerves contain the norepinephrine transporter (NE-t) and tyrosine hydroxylase (TH). Therefore, immunofluorescence labeling for CGRP and NE-t/TH can act as a way to quantify the concentration and distribution of the afferent and efferent nerves, respectively. To our knowledge, no study has examined the distribution of afferent and efferent nerves in the branch RAs, and only one study has studied the renal histopathology after denervation of the RA, which showed suboptimal denervation of the renal nerve fibers because the renal nerves were deeper than depth that could be reached with ablation. Therefore, in studies demonstrating greater BP reduction with ablation of the RA and its branches, it is not known whether this reflects that the RA branches have a greater number of afferent nerves, nerves that are in close proximity to the lumen and thus more amenable to ablation, or a combination of both.

Immunofluorescence labeling was used in the RAs of a human autopsy study, which showed a predominance of efferent nerve fibers with very few afferent fibers. In stark contrast, histopathologic studies demonstrate that in the renal collecting system, the majority of fibers controlling sympathetic tone are afferent nerves. Within the renal pelvis, there are also efferent nerves, and afferent and efferent nerves often intertwined. If it is afferent nerve ablation that is primarily responsible for BP reduction in RDN, it makes sense to target the renal pelvis where they predominate. We therefore developed NephroBlate™ (Verve Medical, Scottsdale, AZ), a radiofrequency catheter system that is introduced trans-urethrally into the renal pelvis, using standard urological techniques, and exploits both the proximity of the renal nerves to the renal pelvis, as well as the preponderance of afferent nerve fibers (Figures 1 and 2). We first tested the NephroBlate™ in a swine model, and found that swine
undergoing ablation had a 60.4% reduction in renal cortical NE levels compared to control. Again, while not specific for afferent nerve ablation, due to the proximity of afferent and efferent nerves, and the high proportion of afferent nerves in the renal pelvis, we can surmise that there was also significant destruction of the afferent nerves with ablation. Histopathologic analysis also confirmed nerve ablation in the treated zones. We next took this proof-of-concept and applied it in a human study. At a urologic center in India, nine patients who had renal disease, and in whom nephrectomy was planned, underwent RDN with the NephroBlate™, followed by nephrectomy 1 month later. Histopathology demonstrated superficial nerves that were fully ablated in treated areas. We then treated four patients with resistant hypertension, and found their BP dropped by a mean systolic of 44 mmHg and a mean diastolic of 18 mmHg. This BP effect was noticed within minutes of treatment in all cases. RDN via a trans-urethral approach also has the advantage of avoidance of systemic contrast, anti-platelet, or heparin administration, an important consideration in patients with chronic kidney disease or bleeding diatheses.

The study by Sakaoka et al is important in that it demonstrates the safety of RDN of the RA and its branch arteries. However, in regards to which approach would better ablate the afferent nerves, and thereby have the potential for a greater effect on BP reduction, we believe RDN via trans-urethral ablation of the renal pelvis merits further exploration.

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FIGURE 1 The NephroBlate™ device with its helical probe [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 2 Cinematography of the NephroBlate™ device in the swine renal pelvis
REFERENCES


