Residual Sympathetic Responsiveness After Catheter-Based Renal Denervation
Lessons From Renal Nerve Stimulation

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The renal nerves play a dominant role in blood pressure (BP) regulation. The intricate interplay between afferent sensory nerves, efferent sympathetic nerves, and modulatory influences mediated by mechano- and chemoreceptors render the renal nerves an attractive therapeutic target.1 Indeed, elegant experimental studies in a range of animal models1 and application of radiotracer dilution to assess spillover of noradrenaline released from sympathetic nerves to plasma2 have provided unequivocal evidence for a strong neurogenic component of the BP rise in patients with hypertension. In animal experiments, surgical denervation of the kidneys was used primarily to gain a better understanding of their role in regulation of renal function and BP control. However, the idea of targeting sympathetic nerves therapeutically including those innervating the kidneys was soon introduced clinically to treat patients with nephritis3 and severe hypertension,4 most commonly by splanchnicectomy. Although more invasive, surgical denervation has the advantage of a high likelihood of achieving complete denervation. In contrast, intraluminal catheter-based renal denervation approaches currently in use after reappraisal of the therapeutic concept for patients with resistant hypertension are limited by the inability to assess and confirm whether adequate denervation has actually been achieved.5 Indeed, insufficient or incomplete denervation has been proposed as a likely factor contributing to the variable BP response to renal denervation and the failure of Symplicity HTN-3 to demonstrate efficacy beyond that of a sham procedure.6

In this issue of Hypertension, de Jong et al7 present findings from a small patient series that further supports the notion that incomplete denervation may indeed represent an important determinant of the BP response to renal denervation. Building on their previous work the authors applied electric stimulation with a quadripolar catheter at 4 sites within each main renal artery both before and after catheter-based renal denervation.7 Intra-arterial BP measurements were taken at the end of a 1-minute renal nerve stimulation cycle. The substantial increase in BP in response to renal nerve stimulation in the main renal arteries observed before renal denervation (+31.5±14.1 mm Hg) was significantly blunted, albeit not completely abolished, when stimulation was repeated after denervation (+9.2±5.3 mm Hg). Of note, in this study, renal denervation was performed with 2 different radiofrequency ablation systems, one being a single-electrode device (used in 12 patients), the other a multielectrode one (4 electrodes; used in 9 patients) with a maximum of 12 ablations (n=3 treatments) per artery with the latter. The residual response to renal nerve stimulation in the main artery after ablation may in its own right be considered as an indication of suboptimal or incomplete denervation given that an almost identical approach in a canine model in which 5 treatments with a quadripole-electrode catheter (n=20 ablations per artery) were performed,8 demonstrated complete absence of a BP response to renal nerve stimulation after denervation.

Most relevant, however, in the current context are observations obtained from 9 patients who had an accessory renal artery with a diameter too small to be ablated.7 In 6 of these patients, the authors were able to perform renal nerve stimulation in the accessory renal artery and found that the BP response elicited by stimulation of renal nerves in the accessory artery was unchanged before and after ablation of the main renal artery. Clearly, and in line with data from the aforementioned canine model,4 this study demonstrates that sympathetic responsiveness to relevant stimuli is maintained in nonablated accessory renal arteries and could well contribute to the variable BP response to renal denervation. Along the same lines it would appear likely that larger branches originating from the main renal artery that are left untreated could behave similarly and blunt the BP response to renal denervation.9 Indeed, the recent demonstration of a more marked reduction in renal noradrenaline content with ablation approaches including branches of the main renal artery10 supports this notion and indicates that more complete ablation may be warranted.

As much as the described residual sympathetic responsiveness in nonablated renal accessory arteries is of interest, the authors unfortunately did not produce what seems to be
critical data, namely whether the response to renal nerve stimulation predicts the BP response to renal denervation, thereby failing to provide at least some evidence for a cause–effect relationship. Future studies will have to address this issue.

From a practical point of view, although renal nerve stimulation seems feasible, the requirement of general anesthesia for a procedure that is otherwise easily performed with conscious analgosedation raises concerns in regard to a potentially increased periprocedural risk for patients, increased costs, and logistical aspects. Furthermore, interpretation of the changes in BP responses to electric stimulation before and after renal denervation will be difficult in individual patients, and algorithms would have to be developed to allow identification of a minimum reduction in the BP response to stimulation required to predict a relevant BP reduction after renal denervation. The site of stimulation may also elicit varying responses. Finally, general anesthesia may influence the responses to renal nerve stimulation with possible variation between individual patients. Taken together, the issues raised do question the practicality of this specific approach in a clinical environment, even if most of the open questions could be addressed. Furthermore, it remains unexplored which therapeutic consequences should ensue if residual sympathetic responsiveness was detected, particularly when proper circumferential ablation has been performed.

Nevertheless, de Jong et al are to be commended for their efforts to investigate the changes in sympathetic responsiveness with renal denervation and providing new insights into potential mechanisms underlying the variable BP response. This is merely the beginning of a new avenue of clinical research in the renal denervation field that may not only help to better understand the variability in response rates but also facilitate optimization of our current therapeutic approaches.

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