Electric Nerve Stimulation to Monitor the Efficacy of Renal Denervation

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In 2009, Krum et al.1 reported a substantial blood pressure decrease (~27/17 mm Hg at 12 months) after percutaneous radiofrequency catheter-based renal sympathetic denervation in a cohort of 45 patients with resistant hypertension. One year later, the results of this proof-of-concept study were confirmed in 106 resistant hypertensive patients randomized 1:1 to renal denervation plus previous drug treatment versus drug treatment alone, with a blood pressure decrease of ~32/12 mm Hg at 6 months in the renal denervation group (P<0.0001), contrasting with virtually unchanged blood pressure in the control group (SYMPLICITY HTN-2).2 However, the SYMPLICITY studies have important limitations, addressed in detail elsewhere.3 Accordingly, there is a growing consensus that renal denervation should remain the ultima ratio in resistant hypertension3 and should only be administered by multidisciplinary teams in tertiary referral centres, after careful patient selection.

Unfortunately, besides higher baseline systolic blood pressure and use of central sympatholytic agents,4 SYMPLICITY studies failed to identify independent predictors of blood pressure response after renal denervation. Therefore, patient selection is almost entirely based on negative criteria, such as exclusion of patients with secondary and white coat hypertension or with narrow or too short renal arteries. In individual cases, whether lack of blood pressure decrease after renal denervation is due to poor contribution of the sympathetic system to the pathogenesis or the maintenance of hypertension, or failure to denervate the kidneys in an effective manner remains elusive. Simple and early measures of technical success are thus urgently needed.

Activity of the afferent and efferent nerves cannot be quantified directly in humans. We are limited to assess downstream effects. Several options have been explored. In this perspective, norepinephrine renal spillover measured by the isotope dilution method 15 to 30 days after renal denervation in a subset of 10 patients from SYMPLICITY HTN-1 lowered by an average of 47% (95% confidence interval, 28–65). In a patient with resistant hypertension, Schlaich et al.5 also reported halving of renin activity, increased renal plasma flow, decrease of norepinephrine kidney and whole body spillover, reduction in muscle sympathetic nerve activity (MSNA), and improved baroreflex sensitivity. In contrast with this case report, in 11 patients with resistant hypertension, Brinkmann et al.6 observed neither significant blood pressure decrease nor decrease in MSNA or baroreflex control of heart rate 3 to 6 months after renal denervation. Furthermore, there was no correlation between the changes in systolic blood pressure and changes in MSNA or plasma norepinephrine.6 However, a major limitation of this study is that all patients were on multiple antihypertensive medications potentially affecting MSNA, making it difficult to identify the net effect of renal denervation on MSNA.

Albeit preliminary, the study by Chinushi et al.7 published in this issue of Hypertension may pave the way toward a simpler method to assess the efficacy of the technique in the Cath laboratory, derived from the experience of electrophysiologists. In patients with atrial fibrillation undergoing pulmonary vein isolation, selective endocardial electric stimulation by an ablation catheter at the presumed anatomic sites of epicardial autonomic ganglia in the vicinity of pulmonary veins may elicit a vagal response defined as transient cardiac asystole, atrioventricular block, an increase in mean RR interval >50% during atrial fibrillation, or a sudden decrease in blood pressure (>20 mmHg). In some patients, this parasympathetic response is abolished by pulmonary vein isolation, reflecting the contribution of ablation of these autonomic ganglia, that is, parasympathetic denervation, to the efficacy of pulmonary vein isolation for the prevention of recurrent atrial fibrillation.

The authors had the ingenious idea to apply this concept to the field of renal denervation. They hypothesized that electric stimulation of (this time ortho-) sympathetic fibers located in the adventitia of renal arteries would elicit an orthosympathetic response. Attenuation or abolition of the different components of this response by renal denervation might reflect effective destruction of a significant proportion of fibres, that is, technical success of renal denervation. Chinushi et al adopted a rather straightforward approach. Using an open irrigation electrophysiology catheter, they performed unilateral renal artery nerve ablation by radiofrequency in 8 anesthetized dogs from 0 to 10 mm from the ostium. Within this segment, they subsequently applied electric currents similar to those used.
to stimulate autonomic heart ganglia in patients with atrial fibrillation.\(^5\)\(^9\) both before and after renal denervation. And as, according to Louis Pasteur, chance often favors the prepared mind, it worked!

Indeed, before renal denervation, electric stimulation was followed by significant increases in blood pressure, heart rate, and heart rate variability, as well as plasma epinephrine and norepinephrine, and after the procedure these responses were significantly blunted in the denervated renal artery, but remained basically unchanged after application of the same currents to the contralateral intact artery.

This study demonstrates that the systemic hemodynamic response to electric nerve stimulation can be used to monitor the efficacy of endovascular renal denervation, at least in an animal model. Furthermore, it provides new insights into the pathophysiological mechanisms underlying the effects of both electric stimulation and renal sympathetic nerve ablation. First, the acute systemic increase in blood pressure, heart rate, and heart rate variability attributed to electric stimulation likely reflects systemic vasoconstriction. A direct vasoconstrictive effect of electric autonomic stimulation was unlikely because blood pressure increased only 15 to 30 seconds post-stimulation and did not occur in the contralateral denervated artery. Second, in the absence of sympathetic nerve connections between renal ganglia and adrenal gland, the primary source of epinephrine, the rise of epinephrine elicited by electric stimulation of intact renal arteries suggests involvement of afferent (rather than efferent) sympathetic nerves. Accordingly, the observation that renal denervation prevents this increase in serum epinephrine levels may indicate that afferent pathways indeed contribute to the blood pressure response to renal denervation.

Although borrowed from the cardiac electrophysiologists, the approach presented in this article\(^7\) is innovative in the field of nephrology and hypertension and deserves to be further explored. Future work should aim to assess its safety and efficacy in nonanesthetized resistant hypertensive patients treated by currently approved renal denervation systems, and to determine the most suitable target site of electric stimulation and characteristics of currents required to elicit the effect. Furthermore, electric stimulation may prove a valuable tool to dissect the mechanisms underlying the effects of renal denervation and to test new protocols of renal nerve ablation, catheters and energy sources, either alone, or in combination with other approaches, such as noninvasive assessment of heart rate variability by power spectral analysis.\(^10\)

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**References**
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