Renal Nerves: Time for Reassessment of Their Role in Hypertension?

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Catheter-based renal nerve ablation (CBRNA) is a promising new approach to reducing blood pressure in human patients with drug-resistant hypertension.¹ The concept behind the method was derived from many decades of work in laboratory animals that showed the significant effect of renal nerves on blood pressure regulation in experimental hypertension and the physiological mechanisms underlying that effect.² Early indications of efficacy of CBRNA in human trials, however, led to an explosion of interest in the procedure and its rapid application to thousands of patients worldwide.³ Most studies have appropriately focused on the clinical efficacy and safety of the procedure. On the other hand, comparatively little attention has been paid to identifying the specific physiological mechanisms responsible for the persistent fall in blood pressure seen in some (but not all) patients.

A highly publicized recent report⁴ on the first prospective, double-blind, randomized, sham-controlled trial in patients with severe resistant hypertension (Symplicity HTN-3) showed that CBRNA failed to lower blood pressure significantly more than a sham procedure. The report has re-energized consideration of the physiological conditions under which the renal nerves are most likely to affect blood pressure in hypertension and the mechanisms responsible. It also has brought to the forefront questions about precisely how much renal nerve damage is necessary to meaningfully affect blood pressure in hypertensive subjects. Two articles appearing in this issue of the Journal, one by Henegar et al.⁵ and one by Linz et al.,⁶ report data from experimental animal studies that shed significant new light on these issues.

The most directly germane is the study by Henegar et al.⁵ These investigators used a well-characterized dog model of hypertension and a catheter device designed for human applications (St. Jude Medical EnligHTN system) to investigate the acute and chronic effects of renal denervation on blood pressure and other relevant physiological variables. Several valuable features of the study design deserve mention. First, renal denervation was performed in dogs with established hypertension. In most previous work on renal denervation in laboratory animals, denervation was done before the onset of hypertension. The approach used by Henegar et al. is more clinically relevant and recognizes the well-known fact that many interventions that mitigate hypertension development have little or no effect on blood pressure once hypertension is established. Second, the dogs were made hypertensive by high-fat feeding; this has clinical relevance because many patients with drug-resistant hypertension are overweight.⁷ Third, the investigators did a thorough job of quantifying the damage to the renal nerves caused by the ablation procedure using both histology and measurement of renal content of norepinephrine. This is important because at present it is not clear how much damage to the renal nerves is necessary to affect blood pressure, and similar quantification is not possible on a routine basis in the clinical setting. Last, but not least, blood pressure measurements were performed using repeated sampling for 18 hours a day for the duration of the study. This kind of recording (roughly equivalent to ambulatory measurements in humans) is critical to detect the small changes in blood pressure typically seen after renal denervation.

The main findings of the Henegar et al. study were that CBRNA lowered BP significantly and persistently in obese hypertensive dogs without a major change in renal function and that this was associated with relatively modest damage to the renal nerves (approximately 42% loss as assessed by histology or norepinephrine content). Although the experiments were not designed specifically to explore the mechanisms responsible for the fall in blood pressure, some of the data collected are informative. No significant changes in heart rate, glomerular filtration rate, plasma renin activity, extracellular fluid volume, plasma volume (estimated from plasma protein concentration), plasma aldosterone, or plasma cortisol were found after CBRNA. Interestingly, the fall in blood pressure did not reach a peak steady-state value until several days after the procedure, suggesting the involvement of more slowly acting blood pressure control mechanisms.

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mechanisms. Similarly detailed time-course data are virtually absent from clinical studies.

It is of substantial importance that only partial loss of renal nerve integrity was required to significantly reduce blood pressure in this study. Moreover, there was a trend (although not statistically significant) for the antihypertensive effect of CBRNA to correlate with the degree of denervation. A noteworthy limitation of all human trials of CBRNA to date (including Symplicity HTN-3) is a lack of data on the completeness of denervation. The little evidence we have in human patients indicates that denervation is far from complete, even when the procedure is performed by experts. This could be a major factor in explaining why blood pressure responses vary widely between patients.

A logical (although not necessarily correct) assumption is that the magnitude of fall in blood pressure after CBRNA in any given subject will depend on the degree to which their blood pressure is being controlled by physiological mechanisms responsive to renal sympathetic nerve activity (RSNA) (e.g., renin release, sodium reabsorption, and renal vascular resistance). Elegant investigations in human subjects by Esler and colleagues reveal that RSNA is increased in some, but not all, patients with essential hypertension. To our knowledge there is no direct evidence for renal sympathetic overactivity in drug-resistant hypertension, but such patients often are obese, and many obese individuals have elevated RSNA. One clear link between obesity, sympathetic overactivity, and hypertension is obstructive sleep apnea (OSA), a prevalent condition in patients with drug-resistant hypertension. Therefore it is important to determine the impact of the renal sympathetic nerves on physiological responses to OSA, including systemic blood pressure. This was the goal of a paper by Linz et al. They used an acute model of OSA in anesthetized pigs that involved repetitive obstruction of the trachea with negative pressure (NTP) every 15 minutes for 4 hours. They continuously recorded blood pressure and renal and femoral blood flow and determined plasma renin activity, plasma aldosterone, urinary protein/creatinine ratio, and glomerular filtration rate several times during the 4-hour protocol. In a subgroup of pigs, the effects of NTP were investigated after renal denervation was performed using the standard surgical approach of stripping away visible nerves and applying a phenol solution to the perivascular region. Another group of pigs was pretreated with the angiotensin receptor blocker irbesartan before being subjected to NTP. The results were striking: although the interapneic values of the measured variables were not affected by renal denervation, the marked postapneic increases in blood pressure and renal vascular resistance seen in untreated pigs were significantly attenuated by renal denervation (but not by irbesartan). Likewise, the gradual increments in plasma renin activity, plasma aldosterone, and urinary protein/creatinine ratio seen in control pigs during repetitive NTP were nearly eliminated in pigs with renal denervation.

Although this was an acute protocol and renal denervation was surgical rather than by catheter, the results highlight some important issues discussed earlier. First, the findings support the common-sense view that the magnitude of any physiological response to renal denervation will depend on the level of renal sympathetic activity at the time of denervation. Accordingly, identification of patients likely to respond to CBRNA should include consideration of other pathologies (such as obesity and OSA) that are associated with increased RSNA. Second, it is notable that a large component of the systemic blood pressure response to NTP appears to depend on neurogenic changes in renal vascular resistance (femoral resistance changed very little). This suggests that under some conditions the mechanism of the antihypertensive response to CBRNA may simply be a reduced contribution of the renal vasculature to total peripheral resistance. Of course the impact of renal denervation on hormones and renal injury in this study also identify other potential mechanisms by which renal nerves could influence long-term blood pressure regulation.

Collectively these articles show that well-designed, animal-based experimental physiology can importantly complement the results of clinical trials and clinical research in our efforts to establish the clinical utility (if any) of CBRNA in treating hypertension.

DISCLOSURE

Dr. Osborn is a paid consultant to Medtronic. Dr. Osborn and Dr. Fink have received financial reimbursement and honoraria from Medtronic for attending scientific meetings.

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