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EDITORIAL

Renal nerve ablation: Emerging role in therapeutics

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Renal sympathetic nerves contribute to the development, maintenance and progression of hypertension and related target organ damage. Both efferent and afferent renal nerve activity play a role in these processes. Efferent sympathetic outflow raises blood pressure (BP) by stimulating renin release, increasing tubular sodium reabsorption and reducing renal blood flow, while afferent signals from the kidney modulate central sympathetic outflow and contribute directly to neurogenic hypertension (1–3). Surgical or chemical denervation of the kidney has been shown to delay, prevent or reverse the development of hypertension in a variety of animal models, providing a strong rationale for use of renal denervation in treating human hypertension (4,5). Furthermore, the concept of renal denervation as treatment for human hypertension is not new and even preceded the development of antihypertensive drugs. Non-selective surgical sympathectomy, which also denervates the kidney, was widely performed for the treatment of severe hypertension in the 1940s and 1950s (6–9). However, the procedure was eventually abandoned because of post-procedural complications, e.g. anhidrosis, sexual and urinary dysfunction, orthostatic hypotension and tachycardia, prolonged postoperative recovery and the unpredictability of the results, as well as the development of safe and effective antihypertensive drugs. In recent years, the increasing prevalence of treatment resistant hypertension has stimulated a search for novel therapies, including a return to sympathectomy as a therapeutic approach. Catheter-based renal denervation using radiofrequency ablation techniques has provided a novel invasive, but safe and well tolerated, means of selectively removing both efferent and afferent renal nerves, thus attenuating the neural component of systemic hypertension and effectively reducing BP in patients with resistant hypertension (10).

Studies of the neurohumoral effects of renal nerve ablation in patients with resistant hypertension have elucidated the mechanisms by which the intervention lowers BP and protects target organs (11,12). Radiofrequency ablation of the renal nerves has been shown to produce afferent and efferent renal denervation, with reductions in central sympathetic outflow, renin release and BP. Denervation effectively reduced renal norepinephrine spillover from elevated pretreatment levels in resistant hypertension patients, indicating that the procedure inhibits efferent renal nerve activity. The decrease in renal efferent nerve activity was accompanied by a reduction in plasma renin activity and an increase in renal plasma flow. Whole-body norepinephrine spillover and muscle sympathetic nerve activity, assessed from the peroneal nerve by microneurography, were reduced from elevated to normal levels at 1 year post-ablation, providing evidence that reduction in afferent renal nerve activity led to a sustained reduction in a central sympathetic outflow. Cardiac baroreflex sensitivity was also improved, left ventricular mass was reduced and office BP was normalized at 1 year despite withdrawal of two antihypertensive drugs. Building on these mechanistic studies, an impressive series of clinical trials have demonstrated that bilateral catheter-based renal nerve ablation is safe and effective in lowering BP in patients with resistant hypertension (11–14). The reductions in BP appeared to be progressive and persisted at 2 years of follow-up.

Exciting presentations at the 21st European Meeting on Hypertension and Cardiovascular Prevention in Milan shed new light on what has been accomplished with radiofrequency renal nerve ablation and

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what may be expected in the future. Discussions focused on in-depth analyses of the long-term neural and hemodynamic effects of renal denervation in patients with resistant hypertension, as well as exploratory use of renal nerve ablation in other conditions in which the sympathetic nervous system is activated. Presentations by Baudrie and Ukena examined the effects of renal sympathetic denervation on BP variability and baroreflex sensitivity, as well as cardiorespiratory responses to exercise, critical issues if this mode of therapy is to be applied widely in the hypertensive population. A series of presentations by Markus Schlaich demonstrated the utility of catheter-based renal nerve ablation in a variety of clinical conditions, including the polycystic ovary syndrome (PCOS), obesity, insulin resistance and end-stage renal disease. In all of these conditions, renal denervation was associated with sustained reductions in central sympathetic outflow and improvement in insulin sensitivity.

The PCOS, characterized by ovarian dysfunction, infertility, androgen excess, obesity, the metabolic syndrome, insulin resistance and hypertension, has an estimated prevalence of 10–18% among women of reproductive age and has emerged as a major cardiovascular risk factor (15,16). Studies have demonstrated increased sympathetic nervous system activity in these patients that is related to the clinical severity of the syndrome (17). These observations are consistent with the concept that chronic sympathetic activation predisposes to development of insulin resistance, hyperinsulinemia and other features of the metabolic syndrome (hypertension, obesity) that are characteristic of the PCOS (18,19). Animal studies have carried this concept further by providing evidence that activation of ovarian sympathetic nerves can produce abnormalities similar to those seen in the human PCOS and that these can be reversed by ovarian sympathectomy (20,21). At ESH 2011, Schlaich reported on the effects of renal denervation via percutaneous endovascular radiofrequency ablation in two young women with PCOS and resistant hypertension (22). Sympathetic nerve activity assessed by microneurography and whole body norepinephrine spillover was elevated (2.5–3 times) at baseline in both women and was reduced by renal nerve ablation. Insulin sensitivity assessed by euglycemic hyperinsulinemic clamp and BP improved following renal denervation. Glomerular hyperfiltration and microalbuminuria were present at baseline and responded favorably to renal denervation. These provocative hypothesis-generating case studies suggest that increased sympathetic nerve activity plays a pivotal role in the pathogenesis of PCOS and that modulation of sympathetic activity by renal denervation may be useful in its treatment.

In a separate presentation, Schlaich provided further evidence of the metabolic benefit of renal denervation in patients with resistant hypertension. At 3 months after renal denervation, significant reductions in fasting glucose, insulin and C-peptide levels, and improvements in oral glucose tolerance and in insulin sensitivity indexed by homeostasis model assessment–insulin resistance (HOMA-IR) were observed, in concert with impressive BP lowering (23). These findings suggest that renal denervation may provide benefit beyond BP reduction in patients with resistant hypertension and metabolic disorders who are at high cardiovascular risk.

Finally, the ESH Working Group on Blood Pressure and Heart Rate Variability sponsored a symposium on Renal Denervation and Reflex Blood pressure Control that included presentations on Reflex regulation of renal sympathetic activity and blood pressure, by P. van de Borne; Renal denervation and neurohumoral control of blood pressure, by M. Schlaich; Renal denervation and blood pressure variability, by M. Azizi; The Denervation of rEnal sympathetic Activity and hypertension (DEPART) study, by P. van de Borne; and Future ideas for research, by G. Parati. In view of the broad spectrum of chronic diseases to which activation of the sympatho-renal axis is thought to contribute, possibilities for future research and for real clinical benefit from selective renal denervation are vast and extremely exciting (24–26). Importantly, widespread interest in this procedure will undoubtedly have a "bedside to bench" effect and stimulate much needed research on neural mechanisms of hypertension and related cardiovascular disease in humans.

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