Renal Sympathetic Denervation

A Novel Intervention for Resistant Hypertension, Insulin Resistance, and Sleep Apnea

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E ffects of renal sympathetic denervation on blood pressure, sleep apnea course and glycemic control in patients with resistant hypertension and sleep apnea” by Witkowski et al is an illuminating report. The authors confirm that renal denervation lowers blood pressure (BP) in patients with stage 2 (BP ≥160/≥100 mm Hg) treatment-resistant hypertension adherent to optimal doses of ≥3 antihypertensive medications, including a diuretic. Their report also endorses the work of Mahfoud et al documenting that renal denervation in humans improves indices of insulin action and glucose metabolism. It should be noted, however, that glycosylated hemoglobin levels declined significantly among patients in the current but not the previous report. The current publication extends previous work by documenting that the BP and metabolic benefits of renal denervation include patients with sleep apnea. However, this is not surprising, because most hypertensive patients with treatment-resistant hypertension have sleep apnea, and it is unlikely that renal denervation would have been effective in previous studies if benefits did not extend to patients with sleep apnea.

The novel aspect of the current work is that renal sympathetic denervation improved sleep apnea in 7 of 8 patients with obstructive sleep apnea and 1 of 2 patients with both obstructive and central components. Although the mechanism(s) by which renal denervation may improve obstructive sleep apnea is unknown, the authors’ hypothesis that changes in sodium-volume status are involved coincides with the literature. The renal sympathetic nerves play an important role in sodium homeostasis, with renal nerve activation enhancing sodium retention and vice versa. In addition, Friedman et al reported last year in Hypertension that patients with treatment-resistant hypertension had a greater shift of fluid from the legs to the neck overnight (recumbent) than patients with controlled hypertension. The volume of leg fluid displaced overnight explained ~56% of the variance in the apnea-hypopnea index. A decrease in extracellular fluid volumes and a reduction in rostral fluid shifts with recumbent sleep may account for the similar reported benefits of aldosterone antagonists and renal denervation on the apnea-hypopnea index. As the authors note, renal denervation may also enhance venous compliance, which could mitigate the rise in capillary-venous pressures in laryngopharyngeal tissues with changes from the upright to the recumbent position.

Several publications documented that patients with resistance to insulin-mediated glucose disposal are more likely to have treatment-resistant hypertension. Although the mechanisms by which renal denervation improves insulin action are unknown, several factors may contribute, including a decrease in vascular α-adrenergic tone, leading to an improved distribution of skeletal muscle blood flow, decreased activity of the renin-angiotensin system, improved early phase insulin response, enhanced sensitivity to insulin’s nonesterified fatty acid–lowering actions, changes in glucose transporters and glucagon secretion, decreased gluconeogenesis, and potentially longer-term increases in muscle-fiber capillary density and changes in muscle-fiber type. It is not possible within the context of this limited commentary to provide more detailed referencing and rationale for the multiple and complex mechanisms by which renal denervation could improve insulin action. More importantly, regardless of mechanism, the fact that renal sympathetic denervation reduces insulin resistance and improves glucose metabolism, while lowering BP, has added potential to reduce macrovascular and potentially microvascular complications in a high-risk patient group.

Although the article by Witkowski et al confirms the BP-lowering effects of sympathetic renal denervation on clinic and ambulatory values, the comparatively large discrepancy between the effects on clinic and ambulatory BP is noteworthy. In the current study, renal denervation lowered office BP 34/13 mm Hg and 24-hour systolic BP 6 mm Hg and 7 mm Hg daytime (not significant) in all 10 of the subjects. Twenty-four-hour BP declined 8/4 mm Hg (median change 24-hour BP, P<0.05) among the 8 patients with a reduction in the apnea-hypopnea index. Baseline office BP was 173/106 mm Hg, whereas daytime ambulatory BP was 147/87 mm Hg. On average, this group had daytime ambulatory BP that was 26/19 mm Hg lower than their office BP. In Symplicity-2, renal denervation lowered office BP 32/12 mm Hg (n=49) and 24-hour ambulatory BP 11/7 mm Hg (n=20). The magnitude of difference between the office and ambulatory BP changes reported with renal sympathetic denervation is rarely seen with antihypertensive medications that have a 24-hour effect with trough:peak ratios >0.5.
As an aside, it is also interesting to note that baseline mean nighttime ambulatory BP among the 10 patients in the current study was 128/76 mm Hg versus daytime 147/87 mm Hg.1 On average, this overweight and obese patient group with treatment-resistant hypertension and documented sleep apnea had a nocturnal decline of 19/11 mm Hg, which is >10%. Thus, at baseline this group cannot be characterized as nondippers.

An article by de la Sierra et al8 earlier this year in Hypertension indicated that ≈3 in 8 patients with treatment-resistant hypertension based on office BP had normal ambulatory BP values or white-coat resistance. The data from Symplicity-2 and the current report raise the possibility that a substantial portion of the BP response to renal sympathetic denervation reflects a decrease in the office or white-coat effect. Although unlikely, another possibility is that the procedure, rather than renal denervation, per se, attenuates the office BP effect. If further research confirms that this intervention reduces BP reactivity and potentially BP variability, then additional benefits on cardiovascular outcomes may accrue, because BP variability is independently linked with clinical events.10,11

Renal sympathetic denervation is a novel intervention in hypertension management and a highly instructive tool for understanding the role of renal sympathetic nerves in health and disease. It should be noted that the reported effects of renal sympathetic denervation likely involve both the efferent and afferent limbs.12 In addition to its antihypertensive effects, the favorable impact of renal denervation on insulin action, glucose metabolism, and sleep apnea strengthens evidence linking sympathetic activation to risk factor clustering. The findings provide new insights into mechanisms of disease and raise the potential for renal sympathetic denervation and other novel autonomic interventions for the growing worldwide population of overweight and obese individuals with the cluster of insulin resistance, resistant hypertension, and sleep apnea.

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