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Renal Sympathetic Denervation: A novel intervention for resistant hypertension, insulin resistance and sleep apnea

Brent M. Egan, MD
Department of Medicine, Medical University of South Carolina, Charleston, SC

Keywords

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"Effects of renal sympathetic denervation on blood pressure (BP), sleep apnea course and glycemic control in patients with resistant hypertension and sleep apnea" by Dr. Witkowski and colleagues is an illuminating report.[1] The authors confirm that renal denervation lowers 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.[2,3] Their report also endorses the work of Mahfoud and coworkers documenting that renal denervation in humans improves indices of insulin action and glucose metabolism.[4] It should be noted, however, that glycosylated hemoglobin levels declined significantly among patients in the current but not the previous report.[1,4] The current publication extends previous work by documenting the BP and metabolic benefits of renal denervation include patients with sleep apnea. However, this is not surprising as most hypertensive patients with treatment resistant hypertension have sleep apnea,[1] and it is unlikely that renal denervation would have been effective in prior 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 seven of eight patients with obstructive sleep apnea and one of two patients with both obstructive and central components. While 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.[5] Additionally, Friedman and co-authors 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.[6] The volume of leg fluid displaced overnight explained roughly 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.[1,7]

Correspondence: Brent M. Egan, MD, Medical University of South Carolina, 135 Rutledge Avenue, RT1230, Charleston, SC 29425, Phone: 843-792-1715, FAX: 843-792-0816, eganbm@musc.edu.

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As the authors note, renal denervation may also enhance venous compliance, which could mitigate the rise in capillary-venous pressures in laryngopharangeal 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. While the mechanisms by which renal denervation improves insulin action are unknown, several factors may contribute including a decrease in vascular alpha-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 non-esterified fatty acid lowering actions, changes in glucose transporters and glucagon secretion, decreased gluconeogenesis, and potentially longer-term increases in muscle-fiber capillary densityand changes in muscle-fiber type.[8] 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,[1,4] while lowering blood pressure,[1,2,4] has added potential to reduce macrovascular and potentially microvascular complicationsin a high-risk patient group.

While the paper 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.[1,2] In the current study, renal denervation lowered office BP 34/13 and 24-hour systolic BP 6 mm Hgand 7 mm Hg daytime (not significant) in all 10 subjects. Twenty-four hour BP declined 8/4 mm Hg (median change 24-hr BP, $p<0.05$) among the eight patients with a reduction in the apnea-hypopnea index. Baseline office BP was 173/106, whereas daytime ambulatory BP was 147/87.1.[1] On average, this group had daytime ambulatory BP that was 26/19 mm Hg lower than their office BP. InSymplicity-2, renal denervation lowered office BP 32/12 mm (N=49) and 24-hour ambulatory BP 11/7 (N=20).[2] The magnitude of difference between the office and ambulatory BP changes reported with renal sympathetic denervation[1,2] is rarely seen with antihypertensive medications that have a 24-hour effect with trough-to-peak ratios >0.5.

As an aside, it is also interesting to note that baseline mean night time ambulatory BP among the 10 patients in the current study was 128/76 vs. daytime 147/87.[1] On average this overweight and obese patient group with treatment resistant hypertension and documented sleep apnea had a nocturnal decline of 19/11 mmHg, which is >10%. Thus, at baseline this group cannot be characterized as non-dippers.

A paper by de la Sierra and colleagues earlier this year in *Hypertension* indicated that approximately three in eight patients with treatment resistant hypertension based on office BP had normal ambulatory BP values or 'white-coat resistance'.[9] 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 this intervention reduces BP reactivity and potentially BP variability, then additional benefits on cardiovascular outcomes may accrue as 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 likely involve both

the efferent and afferent limb.[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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