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## A Mechanistic Explanation for the Minimal Impact of Renal Denervation on 24-h Ambulatory Blood Pressure in SIMPLICITY HTN-3



Explanations for the lack of significant lowering of 24-h ambulatory blood pressure following renal denervation in SYMPLICITY HTN-3 (Renal Denervation in Patients With Uncontrolled Hypertension) have been offered, including the unanticipated fall in ambulatory BP in the sham operated group, perhaps as a result of a Hawthorne effect or placebo effect (1). Alternatively, the recognized individual variation in renal nerve anatomy may have led to inadequate renal denervation in a large proportion of patients, because it is not yet practical or routine to confirm successful renal denervation following the clinical procedure (1,2). I would like to offer an alternative explanation, with clinical implications. The majority of patients enrolled in SYMPLICITY HTN-3 were obese, defined as body mass index (BMI) >30 kg/m<sup>2</sup>. The mean BMI in the renal denervation group was 34.2 ± 6.5 kg/m<sup>2</sup>. Although sympathetic nerve activity, including renal sympathetic nerve activity, is known to be elevated in human obesity (3,4), sympathetic activity is *not greater* in obese patients with hypertension compared with those without hypertension. That is, renal sympathetic activation may not play a mechanistic role in the development of hypertension associated with common human obesity. This contrasts markedly with the situation in lean humans. In lean patients with hypertension, renal sympathetic nerve activity is markedly increased compared with lean normotensive humans, in whom renal sympathetic nerve activity is not elevated (5). Renal sympathetic nerve activation may play a central role in the development of hypertension in lean, but not obese, patients. I wonder if a post-hoc analysis (with all the pitfalls of such an analysis) of SYMPLICITY HTN-3 might be illuminating. When stratified by BMI, is

there a lean cohort that particularly benefits from renal denervation?

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### REPLY: A Mechanistic Explanation for the Minimal Impact of Renal Denervation on 24-h Ambulatory Blood Pressure in SIMPLICITY HTN-3



We appreciate Dr. Middlekauff's interest in the results of SYMPLICITY HTN-3 (Renal Denervation in Patients With Uncontrolled Hypertension) and her thoughtful letter suggesting an alternative explanation for the failure to demonstrate a benefit of renal denervation based on ambulatory blood pressure monitoring. The research cited by Esler et al. (1) and Lambert et al. (2) provides interesting evidence that the role of sympathetic nervous system hyperactivity in the etiology of essential hypertension is different between obese and lean patients with hypertension. However, the clinical implications of the difference in sympathetic nerve firing between obese and lean hypertensive patients are unknown.

We undertook a post-hoc analysis of the blood pressure-lowering effect of renal denervation compared with sham control according to tertiles of body mass index (BMI). No differences between renal denervation and sham were found. Further exploration of results in patients with a normal BMI (≤27 kg/m<sup>2</sup>) also revealed no difference between denervation and