

# Ethnicity and sympathetic tone: predictors of the blood pressure response to renal denervation?

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I read with great interest the News & Views article by Schmieder (How should data from SYMPLICITY HTN-3 be interpreted? *Nat. Rev. Cardiol.* **11**, 375–376; 2014).<sup>1</sup> Schmieder provided an excellent overview of the randomized, sham-controlled, single-blinded SYMPLICITY HTN-3 trial,<sup>2</sup> and provided possible explanations why renal denervation did not lower blood pressure in this cohort of patients.

Schmieder stated that several clinical trials on renal denervation “have uniformly demonstrated significant reductions in both systolic and diastolic blood pressure”.<sup>1</sup> However, the studies in which renal denervation failed to lower blood pressure were not cited, including four studies that showed no decrease in office blood pressure after renal denervation.<sup>3–6</sup> An additional seven studies that showed no decrease in 24-h ambulatory blood pressure after renal denervation were also not mentioned.<sup>7–13</sup> Admittedly, patient numbers in these 11 trials were small ( $n = 6–24$ ), and the majority of clinical studies reported have shown a reduction in blood pressure with renal denervation. Nevertheless, being aware of these negative findings is important.<sup>3–13</sup> For example, Fadl Elmula *et al.* reported that in six patients with true resistant hypertension, office blood pressure remained unchanged at 1, 3 and 6 months after renal denervation.<sup>3</sup> This study was the first to use witnessed intake of medication to exclude patients with poor drug adherence. Drug adherence was not verified in the SYMPLICITY HTN trials.<sup>2,14,15</sup>

Schmieder offered several explanations for the negative results of the SYMPLICITY HTN-3 trial. One reason suggested was ethnic differences in response to renal denervation. Unlike previous trials, 26.2% of the study population in the SYMPLICITY HTN-3 trial<sup>2</sup> were African American. Sub-analyses of ethnicity showed that African-American individuals responded poorly to renal denervation compared with non-African-American individuals, who exhibited “a substantial

reduction in mean systolic blood pressure with renal denervation compared with the control group”.<sup>1</sup> However, the difference was no longer significant after adjusting for multiple comparisons.<sup>16</sup> Schmieder also suggested that the operators of renal denervation in the SYMPLICITY HTN-3 trial lacked experience; however, a previous study demonstrated that renal denervation was ineffective even when performed by very experienced operators.<sup>3</sup>

The 11 trials cited above,<sup>3–13</sup> together with the SYMPLICITY HTN-3 trial,<sup>2</sup> clearly demonstrate that renal denervation is not effective for lowering blood pressure in every patient with resistant hypertension, highlighting the need to identify predictors of the blood-pressure response to renal denervation.<sup>17</sup> A major limitation of the reported clinical trials on renal denervation is that the baseline sympathetic tone of patients has not been investigated. Renal denervation was designed to lower blood pressure by inhibiting the increased sympathetic tone commonly observed in patients with hypertension and, therefore, might not be effective in patients whose sympathetic tone is not increased.<sup>18</sup> Muscle sympathetic nerve activity,<sup>19</sup> heart rate variability,<sup>20</sup> and blood-pressure response to electrical stimulation of renal arteries<sup>21</sup> might be useful parameters to investigate sympathetic tone. In the future, we must investigate whether increased sympathetic tone predicts the blood-pressure response to renal denervation. If so, this marker will help to identify patients who are likely to benefit from this therapy, and avoid possible harm to nonresponders.

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#### Competing interests

The author declares no competing interests.

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