Biomarkers for the Prediction of Blood Pressure Response to Renal Denervation

A Long Way to Go

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See related article, pp 984–990

After the publication of the initial experience in patients with hypertension resistant to conventional drug treatment in 2009,1 catheter-based renal denervation has attracted substantial interest not only from the hypertension community, but also from interventionalists and affected patients alike. Five years onward and not to everyone’s delight, renal denervation is now available in many countries throughout the world as an alternative therapeutic option for patients with treatment-resistant hypertension and additional criteria as defined in the Symplicity HTN-11 and HTN-2 studies.2

Although the safety of radiofrequency ablation–based renal denervation procedures seems favorable with only a small number of reports of renovascular or renal compromise thus far, the rate of blood pressure response to renal denervation, typically defined as a reduction in office systolic blood pressure of $\geq 10$ mm Hg,1,2 is more variable, with response rates reported in the range between $\approx 60\%$ and 90%.3,4 An inherent question that arose was whether or not reliable predictors of the blood pressure response to renal denervation could be identified. Such predictors, if available, would not only assist in selecting the most appropriate patients for this interventional approach, but also help to avoid exposing nonsuitable patients to unnecessary risk and optimize the use of health-related funding resources.

Indeed, in the majority of renal denervation studies published thus far, analyses were performed to address the issue of predictors of blood pressure response to renal denervation. Analyses commonly focused on patient factors that may influence this response such as age, sex, body mass index, history of coronary artery disease, diabetes mellitus, chronic kidney disease, baseline glomerular filtration rate, number and types of antihypertensive medications, and more. Technical aspects such as the number of radiofrequency ablations and others have also been investigated. At this stage, most analyses failed to identify factors that could reliably predict the blood pressure response to renal denervation with the exception of baseline systolic blood pressure, which consistently emerged as a predictor of the magnitude of the blood pressure fall after renal denervation.3,6 Impaired cardiac baroreflex sensitivity has recently been suggested to be a predictor but warrants confirmation in larger studies.7

In this context, Dörr et al in the current issue of the journal present some interesting findings pertaining to the potential usefulness of 3 biomarkers as predictors for the blood pressure response to renal denervation. Although somewhat arbitrary, the authors have chosen to investigate biomarkers that have previously been broadly associated with hypertension, endothelial dysfunction, and vascular remodeling. Soluble fms-like tyrosine kinase-1 functions as an endogenous inhibitor of vascular endothelial growth factors, and elevated levels of soluble fms-like tyrosine kinase-1 have been shown to be associated predominantly with hypertensive pregnancy disorders and preeclampsia. Intracellular and vascular adhesion molecules play a role in endothelial- and leukocyte-associated transmigration processes, and elevated levels have been associated with endothelial dysfunction and accelerated progression of atherosclerosis. Measuring the serum concentrations of these 3 biomarkers using commercially available assays in venous blood samples taken at baseline and at 6 months after bilateral renal denervation in a single-center series of 55 consecutive patients with resistant hypertension revealed significantly higher levels of all 3 biomarkers in 46 patients who experienced a reduction in office systolic blood pressure $\geq 10$ mm Hg when compared with 9 patients whose blood pressure reduction was less pronounced. While the levels of all 3 biomarkers were essentially unchanged at 6 months postprocedure in both responders and nonresponders, the baseline levels of each soluble fms-like tyrosine kinase-1, intracellular adhesion molecule-1, and vascular adhesion molecule-1 correlated significantly with renal denervation–induced blood pressure reduction. Analyzing the receiver operating characteristic curve and applying the Youden index to permit selection of optimal threshold values resulted in high positive predictive values of $> 0.9$ for all 3 biomarkers.

Have we finally found the predictive marker(s) that will simplify and optimize the process of patient selection for renal denervation? Probably not yet.

Although the presented data are clearly of interest and may help to bridge an important gap in the context of appropriate patient selection for renal denervation, it is a small study from a single center with all its inherent limitations. Most importantly, confirmation of the predictive value of soluble fms-like tyrosine kinase-1, intracellular adhesion...
molecule-1, and vascular adhesion molecule-1 is required from larger patient cohorts treated in multiple centers, ideally in various regions around the globe. The cutoff values established in the presented study will also require evaluation, particularly in view of the substantial overlap of biomarker concentrations between responders and nonresponders. A potential impact of other factors on baseline levels of these biomarkers, such as the presence or absence of hypercholesterolemia (prevalence of 48% in the responder group versus 78% in the nonresponder group), will have to be investigated. Similarly, antihypertensive drugs have been shown to affect biomarker levels, which may have to be taken into account.9 Interestingly, although nonresponders in the current study had a mean reduction in systolic office blood pressure of 4.6 mm Hg, they had a more pronounced mean reduction in systolic ambulatory blood pressure of around 7 mm Hg (Table 1), which would certainly be considered a clinically relevant blood pressure reduction and therefore raises the question whether these 9 patients can really be classified as nonresponders. Similarly, responders in the current study seem to have experienced ambulatory blood pressure reductions that appear substantially more pronounced (≈22 mm Hg) compared with a larger cohort of 303 patients with true resistant hypertension from 10 Australian and European centers in whom the average systolic ambulatory blood pressure reduction was 10.2 mm Hg at 6-month follow-up.6

Finally, the proposed pathophysiological link between the identified biomarkers and how their levels may relate to a favorable blood pressure response to renal denervation is weak at best. Clearly, endothelial dysfunction is a hallmark of many cardiovascular conditions, including hypertension, and antihypertensive drug treatment has been demonstrated to improve endothelium-dependent vasodilation and reduce markers of endothelial dysfunction. In the current study, however, despite substantial blood pressure reduction in responders, all 3 biomarkers remained unchanged at 6-month follow-up. Furthermore, although there is ample evidence for cross-talk between the sympathetic nervous system and endothelial- and inflammation-related pathways, data linking any of these biomarkers to sympathetic modulation, which clearly occurs with renal denervation,10 are scarce and unconvincing.

Although we are likely to see many more studies reporting on other biomarkers that may be somewhat related to the blood pressure response to renal denervation, their clinical usefulness will have to be critically evaluated. The quest for reliable predictors of the blood pressure response to renal denervation, particularly in the setting of resistant hypertension, will be neither easy nor quick, but is probably a journey worthwhile to be undertaken.

Disclosures

M. Schlaich is supported by a National Health and Medical Research Council Research Fellowship and has received consulting fees, and/or travel and research support from Medtronic, Abbott, Novartis, Servier, Pfizer, and Boehringer-Ingelheim.

References

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Hypertension. 2014;63:907-908; originally published online January 27, 2014; doi: 10.1161/HYPERTENSIONAHA.113.02752

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