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EDITORIAL COMMENT

Future of Renal Sympathetic Denervation in the Treatment of Hypertension*

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In this issue of the *Journal,* Sardar et al. (1) report the results of a meta-analysis evaluating the blood pressure (BP) response to renal sympathetic denervation (RSD) in 6 sham-controlled randomized clinical trials including 3 recently published trials and totaling 977 patients. Compared with sham control, RSD significantly reduced both systolic and diastolic office, 24-h ambulatory, and daytime BP. The authors conclude that these results should guide the design of larger, pivotal trials to evaluate the long-term efficacy and safety of RSD in patients with uncontrolled and resistant hypertension.

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The reductions in the various BPs by RSD compared with sham varied between 1.6 and 6.5 mm Hg (1). The reduction in ambulatory daytime systolic BP averaged 6.1 mm Hg in the 3 second-generation trials compared with 2.1 mm Hg in the 3 first-generation trials, and this difference was significant. The new findings (1) are interesting, although numerous questions arise regarding the future of RSD in the treatment of hypertension.

First, is it appropriate to restrict the current meta-analysis (1) to sham-controlled studies? We have previously meta-analyzed 7 properly randomized controlled trials of RSD in hypertension comprising 985 patients without finding a BP-lowering effect of RSD (2). Further, when updated to 10 trials and 1,173 patients, there was no BP-lowering effect whether trials were sham controlled or not sham controlled (3), or whether BP was measured in the office or as 24-h ambulatory BP. However, several randomized trials were flawed because of methodological weaknesses. The main problem was insufficient control of drug intake, which we pointed out at an early stage (4,5), making RSD patients, sham patients, and other control patients all susceptible to the Hawthorne effect, as well as other investigator- and patient-unspecific effects on BP. Notably, in the 3 so-called second-generation trials, performed under strict control of confounding factors including drug intake (6), the BP-lowering effect of RSD was significant, surprisingly comparable, and averaged about 6 mm Hg, similar to the BP decrease achieved in the French DENERHTN (French Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension) trial (7), which included standardized stepped-care antihypertensive drug treatment. It could even be questioned whether it is appropriate to merge the first generation of 3 sham-controlled trials with the second generation of 3 sham controlled trials as is done in the current meta-analysis (1), in as much as methods changed substantially. Rather, it could be appropriate to say that most first-generation trials were flawed because investigators simply forgot the lesson regarding the Hawthorne effect, and the 3 new trials represent a new beginning, thereof "second generation."

There are numerous other arguments against merging first and second-generation RSD trials in the same meta-analysis. All first-generation trials were performed in patients with so-called treatment-

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resistant hypertension (1-5). In contrast, the 3 second-generation studies included patients with hypertension but without the requirement of treatment resistance (8-10), and in 2 of the studies, even in patients who were kept off drug treatment (8,9). Beyond strict control of drug intake, all other practical methods, including BP measurements, patient selection, and performance of the RSD procedure itself, with new catheter designs and higher number of ablations in the arteries were improved and different in the second-generation compared with the first-generation trials (1,6).

At this stage, it cannot be determined which change in methods was crucial for the consistent BP-lowering effect documented in the second-generation trials (8-10). However, the evidence is now there to conclude that RSD does lower BP in hypertensive patients. This conclusion is consistent with the known contribution of sympathetic overactivity in the pathogenesis of essential hypertension (11).

Although the overall 6-mm Hg BP-lowering effect of RSD observed in the second-generation trials is relatively modest, roughly corresponding to the effect of *1* antihypertensive drug (12), and the associated clinical benefits remain to be formally demonstrated, one should keep in mind that there is a large variability in BP response to RSD, with 20% to 30% of patients experiencing a "dramatic" BP decrease within 3 months after the procedure. Interestingly, this holds true even in patients off medication, supposedly properly denervated (8,9). Therefore, this variability in response to RSD is either not or not only due to changes in drug treatment adherence or technical issues, but may reflect the variable contribution of the sympathetic system to BP elevation in the individual patient (12). Accordingly, we feel that identification of characteristics allowing us to spot these "extreme-responders" (13) should be a priority for the near future. A first approach would be to look for the differences between "extreme responders" versus nonresponders (13) in a single-patient meta-analysis including properly controlled trials with a homogeneous and standardized design, that is, second-generation trials published (8-10) and in progress like REQUIRE (Renal Denervation on Quality of 24-hr BP Control by Ultrasound in Resistant Hypertension) (14), RADIANCE-HTN TRIO (A Study of the ReCor Medical Paradise System in Clinical Hypertension) (NCT02649426), and TARGET BP-OFF-MED (NCT03503773).

Finally, recent evidence from the RADIOSOUND-HTN (A Three-Arm Randomized Trial of Different Renal Denervation Devices and Techniques in Patients With Resistant Hypertension) randomized trial (15), which provided the first head-to-head comparison of 2 different renal ablation systems, suggested that ultrasound-based RSD may elicit a larger BP decrease than radiofrequency-based RSD. Hence, optimized patient selection and technical improvements may allow breaking the "glass ceiling" of 6 mm Hg. Research on RSD still has good days to come, and patients may eventually benefit from this research effort.

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