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EDITORIAL COMMENT

Renal Sympathetic Denervation

Looking Beyond Hypertension*

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Since 2006, endovascular renal sympathetic denervation has been studied as a potential therapy for patients with treatment-resistant hypertension. In the years that followed, numerous studies were published reporting on the remarkable blood pressure-lowering effects of renal sympathetic denervation, generating almost boundless enthusiasm. This sentiment was strengthened by multiple reports showing that the technology could be of tremendous benefit in treating metabolic syndrome, renal failure, obstructive sleep apnea, heart failure, atrial fibrillation, and even polycystic ovary syndrome, suggesting potential pleiotropic effects of the therapy designed to reduce sympathetic nerve activity. Since 2014, however, the results of the sham-controlled Symplicity HTN-3 (Renal Denervation in Patients With Uncontrolled Hypertension) trial overshadowed the initial overwhelming enthusiasm about renal denervation when the trial findings turned out to be negative, and it was concluded that "renal denervation does not reduce blood pressure as compared to a sham procedure" (1). Critics suggested that inadequate denervation by a first-generation device, lack of operator experience, tightening of the medical therapy, and an unexpectedly great effect of the sham treatment were likely reasons for the trial findings to be negative. However, they could not prevent the substantial group of believers in the technology from being shocked. What was left to believe of the large body of positive reports from the years before?

As a consequence, large clinical trials aiming to enroll more than 5,000 patients were canceled, and engineers went back to the drawing board to discuss and improve procedural efficacy. In the meantime, the quest for finding the "responding" patient continues, and current datasets are scrutinized with the aim of finding potential clues to help optimize patient selection and find potential pleiotropic effects of the treatment. In particular, the latter resulted in several interesting observations on specific endpoints, which are potentially less variable than blood pressure.

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Along these lines, in this issue of *JACC: Cardiovascular Interventions*, Schirmer et al. (2) report on left atrial (LA) remodeling after renal denervation and conclude that LA volume index (LAVI) significantly decreases at 6 months post-treatment, irrespective of blood pressure and heart rate. Additionally, a significant decrease in premature atrial contractions (PACs) was observed after treatment, again independent of a change in LAVI—an interesting observation supporting the body of evidence on the pleiotropic effects of renal denervation. In particular, systematic Holter monitoring in patients pre- and post-treatment is interesting and illustrates the persistence of this group of investigators in helping us better understand the potential pleiotropic effects of this black box procedure. The study adds to several previous reports demonstrating a potential decrease in ventricular arrhythmias and renal resistance index and improvement in arterial stiffness (3-6). Improvement in these parameters is in line with what one would expect after an endovascular treatment that significantly decreases systemic sympathetic activity (7). More specifically, they confirm, in vivo, several animal studies showing the effect of denervating the kidney on a more pathophysiological level (8).

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Nevertheless, there are some peculiarities in the study by Schirmer et al. that deserve mentioning. Left atrial (LA) enlargement has been directly correlated with diastolic dysfunction and increased left ventricular filling pressures—a correlation that has been adopted by international guidelines for assessing diastolic function (9). More specifically, in these guidelines, LA volume is one of the parameters determining diastolic function (10). It remains therefore peculiar in the present study by Schirmer et al. that there is no correlation among change in LAVI, diastolic function, and blood pressure as well as a lack of correlation between the change in LA volume and pro-brain natriuretic peptide levels.

In addition, there seems to be some discrepancy in the findings of the present study compared with previous work coming from the same group. In the present study, LAVI, as measured using echocardiography, decreases after renal denervation. However, in previous work, LA volume (measured using magnetic resonance imaging) did not appear to change after renal denervation in the total cohort studied (LA volume changed from 25.7 cm^2 at baseline to 25.3 cm^2 at follow-up, $p = 0.25$) (11). Subsequently, the study raises again the discussion of whether renal denervation reduces heart rate (12). In the present study, renal denervation reduced heart rate at 6 months by at least 8 beats/min. Previous studies showed a decrease of only 2.1 beats/min at 6 months, and neither the randomized Symplicity HTN-3 trial nor the DENER-HTN (Renal Denervation in Hypertension) trial could confirm a reduction in heart rate in patients treated with renal denervation compared with (sham) control groups (1,12,13).

Finally, the authors measured the burden of PACs in virtually all of their patients at baseline and 6 months and found a significant decrease in PACs, but only in patients with the highest number (upper tertile) of PACs at baseline.

After summarizing the current body of evidence, one gets lost. A new technology appears to be safe and effective in reducing blood pressure, and supplementary studies demonstrate that left ventricular mass regresses, diastolic function improves, LA size decreases, and the number of PACs decreases mechanistically, all in line with what one would expect. What remains peculiar, however, is that the vast majority of these pleiotropic effects are only seen in patients with baseline values in the upper tertile, as illustrated by the effect on heart rate, PACs, and LA size. Whether these beneficial findings are truly due to a *pleiotropic* procedural effect or whether *regression to the mean* might have had an impact remains a topic of debate (14). What we are left with today is a technology that was introduced into practice as a simple and safe 30-min procedure with the potential to improve an enormous amount of medical conditions with which the medical community struggled for many years. Merely 9 years after its market introduction, the findings of the first decent sham-controlled, double-blind, randomized, controlled trial appeared to be negative and put the technology back in a development stage, a serious setback that not only resulted in an enormous decrease in the amount of procedures performed worldwide but, most important, decelerated the initiation of larger randomized, controlled studies—studies that are of paramount importance to help us to better understand the true value of this promising new treatment modality. Because it is highly unlikely that the findings of a large number of randomized and observational studies are all false positive, further research on the topic is of paramount importance. Fortunately, new sham-controlled mechanistic studies are currently being designed to provide us with more insights into the true potential of the technology and the characteristics of patients who can benefit from treatment.

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