



EDITORIAL COMMENT

Renal sympathetic denervation – Phenomenon or noumenon?☆



Desnervação simpática renal – fenómeno ou númeno?

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Among percutaneous techniques, renal sympathetic denervation has probably generated the greatest expectations in recent years. The possibility of non-pharmacological treatment of hypertension has aroused interest not only in the medical and scientific community but also in the non-specialist media and the general population. Pilot studies^{1,2} reported results that many considered too good to be true, but despite this skepticism, they were also too good to be ignored, given the large scale of this health problem.^{3,4} The technique is commercially available in many countries and has been applied primarily in patients with resistant hypertension. It is estimated that, two years after the publication of the Symplicity HTN-2 study, over 5000 patients have been treated. The initial experience of centers using the technique has been similar to that reported in the pilot studies,^{5,6} although with a higher but still acceptable rate of non-responders. Registries have been established whose preliminary results have gone some way to validating the method.^{7–9} Another important development has been the widening of selection criteria to include less severe forms of hypertension, which is contrary to the recommendations of medical societies.^{10–14} Nevertheless, even here the results have been favorable in terms of safety and hemodynamic benefits.¹⁵ Other benefits have also been reported,¹⁶ including improvements in glucose metabolism

and diabetic status, left ventricular mass index and diastolic function, reduced recurrence of atrial fibrillation following pulmonary vein isolation, and control of ventricular arrhythmias refractory to medical therapy. Other conditions that are characterized by hyperactivation of the sympathetic nervous or renin–angiotensin–aldosterone systems, such as heart failure, have been suggested as therapeutic targets and clinical trials have begun.¹⁶ Many companies have joined the ‘gold rush’ and developed renal denervation systems using radiofrequency, ultrasound, cryoablation or neurotoxins.¹⁷ Many other systems have appeared on the European market and pilot studies report similar results to the original model.¹⁷

Interest in the technique grew exponentially until January 9, 2014, when the announcement¹⁸ that the Symplicity HTN-3 study had failed to meet the primary efficacy endpoint curbed this enthusiasm. Although details are still awaited, many clinical trials have been suspended (HTN-Japan, HTN-India and Symplicity HTN-4 in the US), as has the activity of many centers. The Symplicity HTN-3 trial¹⁹ was designed to meet the requirements of the US Food and Drug Administration for possible approval. The differences between this and previous Symplicity HTN studies included the larger sample size (530 patients), use of ambulatory blood pressure monitoring in patient selection, and a sham procedure in a control group, blinded to the patients and investigators responsible for blood pressure measurement.¹⁹ The primary efficacy endpoint was whether renal sympathetic denervation reduced office systolic blood pressure at six months, but it did not, which in the absence of additional data has led to much speculation. An important aspect of the trial was the fact that blinding was ended at six months, with control group patients being offered the

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procedure. This invalidates any comparison between the groups in a longer follow-up, which may well be necessary for the placebo effect to wear off. Previous studies suggest that the placebo effect may help control stage 1 and 2 hypertension for 12 months in a third of patients, with a similar adverse effect rate to active treatment.²⁰ The rate of major blood pressure elevation is higher, but this occurred after more than 12 months in over 50% of cases.²⁰ Thus, the placebo effect appears to lose its therapeutic effect over time and a high crossover rate in the Symplicity HTN-3 trial may compromise any analysis. The insignificant difference between blood pressure at baseline and at six months in the group undergoing renal denervation is a more serious concern for the future of the technique. It also calls into question the results not only of the previous Symplicity trials but also of the Global Symplicity Registry, pilot studies using other systems, and single-center registries and experiences like the one by Dores et al. published in this issue of the *Journal*.²¹

What lies behind the conflicting results? In Kant's philosophy, phenomena represent the world as we perceive it, as distinguished from noumena or things-in-themselves, the world that exists independently of our experience. How important are the patient's perception, the investigator's bias and the procedure itself? Is renal sympathetic denervation and associated blood pressure reduction phenomenon or noumenon?

Conflicts of interest

The author has no conflicts of interest to declare.

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