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# New Treatment for Old Disease: Management of Resistant Hypertension by Percutaneous Renal Sympathetic Denervation

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ABSTRACT

Hypertension is a major contributor to cardiovascular events, such as stroke and myocardial infarction, with accelerated sympathetic nerve activity implicated in its pathogenesis. However, hypertension in many patients is not adequately controlled, despite the availability of numerous medication classes. Novel procedure—as well as device-based strategies, such as percutaneous renal sympathetic nerve denervation therapy—have been developed to improve blood pressure in these refractory patients. Renal sympathetic denervation delivers not only a decrease in blood pressure levels but also renal as well as systemic sympathetic nerve activity. The reduction in blood pressure appears to be sustained over 3 years after the procedure, which implies no counterregulatory mechanism or re-innervation of afferent renal sympathetic nerve so far. Renal sympathetic denervation is expected to be a promising treatment for patients with hypertension, congestive heart failure, chronic kidney disease, and metabolic syndrome implicated in the pathogenesis of potentiated sympathetic nerve activity. This review will focus on the current devices and procedures, their outcomes and prospects in the treatment of hypertension.



## Un tratamiento nuevo para una enfermedad antigua: tratamiento de la hipertensión arterial resistente mediante denervación simpática renal percutánea

*Palabras clave:*
Simpatectomía renal
Hipertensión resistente
Actividad nerviosa simpática
Denervación

RESUMEN

La hipertensión es un importante factor de riesgo que contribuye a que ocurran eventos cardiovasculares como el ictus y el infarto de miocardio; en su patogenia está involucrada la actividad nerviosa simpática acelerada. Sin embargo, no se controla adecuadamente la hipertensión de muchos pacientes a pesar de disponerse de múltiples fármacos para tratarla. Se han desarrollado nuevas estrategias basadas en intervenciones y en dispositivos, como la terapia de denervación simpática renal percutánea, para mejorar el control de la presión arterial en estos pacientes refractarios. La denervación simpática renal proporciona una disminución no sólo de la presión arterial, sino también de la actividad nerviosa simpática sistémica. La reducción de la presión arterial parece mantenerse 3 años tras la intervención, lo cual implica que en este tiempo no se produce ningún mecanismo de contrarregulación ni reinervación de los nervios simpáticos renales aferentes. Se espera que la denervación simpática renal sea un tratamiento prometedor para los pacientes con hipertensión arterial, insuficiencia cardiaca congestiva, enfermedad renal crónica y síndrome metabólico, eventos que intervienen en la patogenia de la potenciación de la actividad nerviosa simpática. Esta revisión se centra en los dispositivos e intervenciones actuales, sus resultados y las perspectivas que abren en el tratamiento de la hipertensión.



## GENERAL BACKGROUND

Hypertension is a growing public health problem worldwide as it is a major contributor to cardiovascular diseases such as stroke and myocardial infarction.[1] The estimated overall prevalence of hypertension in adults was 972 million in 2000 but is expected to increase to 1.56 billion by 2025.[2] Approximately 50% of patients with hypertension do not achieve adequate blood pressure (BP) control[2] as observed in studies of awareness, treatment, and control of hypertension. Adequate control of hypertension is a priority because patients with uncontrolled hypertension are at increased risk for cardiovascular mortality, doubling with each 20/10 mmHg increase in BP.[3] However, adequate BP levels are not obtained in many patients, despite compliance with maximum tolerance doses of >3 antihypertensive medications of different classes including a diuretic.[4] This 'resistant hypertension' is estimated to occur in 8.9% of all adults with hypertension and 12.8% of all drug-treated hypertensive adults in the United States.[5] These resistant hypertensive patients clearly need new therapeutic approaches to optimize BP control. Recently, device- and procedure-based therapies have been developed among these

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**Abbreviations**

BP: blood pressure
CNS: central nervous system
RF: radiofrequency
RND: renal sympathetic denervation
SNA: sympathetic nerve activity

populations.[6] A percutaneous, catheter-based renal sympathetic denervation (RND) approach has been proposed to disrupt both afferent and efferent renal sympathetic nerves initially using radiofrequency (RF) ablation (later other modalities) as a therapy for resistant hypertensive patients (Fig. 1).[7]

## RENAL SYMPATHETIC DENERVATION PROCEDURE WITH THE SYMPLICITY™ SYSTEM

The RND procedure is safe and simple, with an average procedure time of 38 min [interquartile range, 34-48 min] shown in the first pilot study.[6] This procedure is performed via the femoral artery with administration of heparin (initially, 5000 units: target active clotting time >250 s) for anticoagulation. First, an aortogram is performed with a 5 Fr-pigtail catheter to confirm the anatomical figure of renal arteries. Once the anatomy is confirmed (appropriate diameter and length, essentially free of atherosclerotic disease), a 6 F LIMA or RDC guiding catheter is used. For the target renal artery for ablation, main renal arteries of ≥4 mm in diameter and ≥20 mm in length are applied. Accessory renal arteries and side branches of the main renal artery with adequate diameter and length might be considered when these are distributed >30% of kidney as a feeding artery. RF ablation at the catheter tip is then applied to the vascular wall to provide heat to the external layer and the sympathetic nerves that arborize around the artery and primarily lie within in the adventitia (Figs. 2A and B). Treatment involves circumferential coverage involving 4 to 6 treatments of low-power RF energy (8 W or less) from the distal point in both renal arteries, lasting ≤120 s and administered in a spiral manner by manual rotation with approximately 5 mm pullback between ablation (Fig. 2A and C). To position the catheter, the tip is placed in the most distal point of each renal artery, and then gradually deflected into the vessel wall until the electrode is well-apposed to the vessel wall. Tip temperature and impedance is monitored in response to a predetermined algorithm during ablation. Higher (~300 Ω) and stable (<20 Ω in change) impedance over the respiratory cycle indicates better wall contact. A larger change in impedance indicates better delivery of energy, but abnormally high impedance and abnormally large change in impedance might suggest the electrode is in a side branch. The target reduction by impedance percentage is approximately −11% to −14%. RF ablation would be canceled when the tip temperature is ≥60 °C, and the change in impedance percentage is exceedingly large.

## EFFICACY AND SAFETY

An initial first-in-man trial (Symplicity HTN-1) evaluated the efficacy and safety of this approach in patients with resistant hypertension (Table).[6] The reduction of postprocedure office BPs was maintained even at 24 months' follow-up without adverse events (reduction of 20/10, 24/11, 25/11, 23/11, 26/14, and 32/14 mmHg at 1, 3, 6, 12, 18, and 24 months, respectively) (Fig. 3).[8] In addition to the reduction in BP, organ-specific sympathetic denervation was demonstrated.[6,9]

However, there was no control group with which to derive a comparison in the Symplicity HTN-1 trial. Therefore, the Symplicity HTN-2 trial, a multicenter, prospective, randomized trial, was performed to address this shortcoming. In this study, significant and sustained reduction in BP at 1 year follow-up was also demonstrated.[10]

Renal function was also evaluated by measuring the level of serum creatinine, based on estimated glomerular filtration rate.

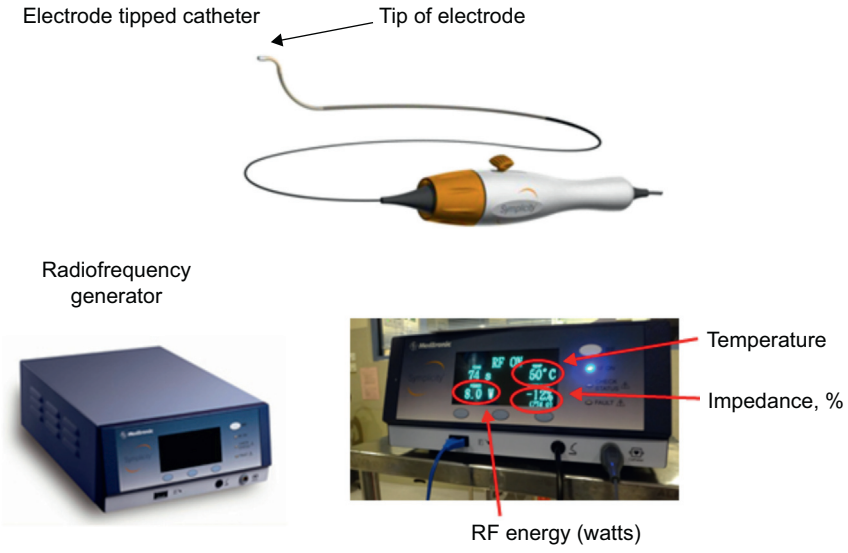


**Figure 1.** Renal sympathetic denervation system Symplicity™. There are 2 components in the Symplicity™ system: the electrode-tipped catheter and the radiofrequency generator. The electrode tip has a low profile, is flexible and self-orienting. The electrode tip delivers radiofrequency energy to the treatment site. The radiofrequency generator is applied to deliver automated and low-power radiofrequency energy to the electrode tip and to monitor the tip temperature and impedance in response to a predetermined algorithm during ablation. RF, radiofrequency. Reproduced with permission from Medtronic Inc.[7]