



What are the benefits of renal denervation in patients with resistant hypertension?

“The recently developed technique of endovascular renal sympathetic denervation revived the historical concept of surgical denervation.”

KEYWORDS: cardiovascular disease ■ prevention ■ renal denervation ■ resistant hypertension

Systemic arterial hypertension is one of the most important public health issues, affecting more than one-quarter of the adult population in industrialized countries [1]. It is a major risk factor for cardiovascular disease morbidity and mortality [2,3]. In most patients, hypertension can be effectively managed by a combination of lifestyle interventions and medication [4]. However, a significant portion of patients treated for hypertension are resistant to therapy. Conventionally, resistant hypertension is defined as persistent elevation of blood pressure above goal levels despite the use of at least three hypertensive agents from different classes, including a diuretic, in optimal doses [5]. Current prevalence estimates suggest that 10–30% of patients with hypertension may be resistant to drug therapy [6].

Renal sympathetic overactivity seems to play a crucial role in the development of arterial hypertension and resistance to treatment. Activation of efferent renal sympathetic nerve fibers results in an increased renin secretion rate, increased renal vasoconstriction and enhanced sodium and water retention [7]. In addition, afferent sympathetic activation from the kidneys to the CNS, seems to enhance sympathetic nerve discharge itself again, leading to a vicious circle in the development of arterial hypertension and cardiovascular morbidity [8]. Both effects, the activation of efferent renal sympathetic nerve fibers as well as the afferent ‘feedback’ from the kidneys seem to play a crucial role in the pathogenesis and maintenance of arterial hypertension. The idea of treating arterial hypertension by targeting the autonomic nervous system is decades old. In the predrug era, treatment of malignant hypertension was limited to surgical approaches, such as nephrectomy and surgical lysis of the autonomic nerves. Nonselective surgical sympathectomy (thoracolumbar splanchnicectomy), the so-called Smithwick intervention, was popular during the

1940s and 1950s [9]. This radical surgical intervention resulted in impressive reductions in blood pressure levels and significant improvement in survival rates. One nonrandomized clinical study from 1938 to 1947 could demonstrate great benefit of splanchnicectomy. The 5-year mortality rate of surgically treated patients (n = 1266) was 19% compared with 54% in the medically treated study group (n = 467) [10]. However, the procedure was associated with major postsurgical morbidity due to sympathetic denervation of the lower half of the body, such as orthostatic hypotension and impotence in men.

The recently developed technique of endovascular renal sympathetic denervation (RD) revived the historical concept of surgical denervation. The catheter-based procedure selectively disrupts renal sympathetic nerves using intraluminal radiofrequency ablation [11]. Initial studies of RD demonstrated substantial reductions in blood pressure without major periprocedural complications [12–14]. Symplicity HTN-1 is the longest running trial investigating the safety and efficacy of endovascular RD in patients with resistant hypertension. Designed as a series of pilot studies in Australia, Europe and the USA, a total of 153 patients with average blood pressure levels of 176/98 mmHg were enrolled in a non-randomized open-labeled fashion. Mean reduction in office-based blood pressure at 2 years was -29/-14 mmHg (n = 105) and at 3 years was -31/-16 mmHg (n = 36). The expanded 2- and 3-year cohort data were presented at the 24th Annual Transcatheter Cardiovascular Therapeutics Scientific Symposium and represent a doubling of the previously reported patient number after 2 years [12]. Following these promising results, the randomized controlled Symplicity HTN-2 trial was performed [13]. The trial included a total of 100 patients that were randomly assigned to RD while continuing prior medical therapy (n = 49) or



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to continue prior medical therapy alone (n = 51). The average reduction in office blood pressure by -32/-12 mmHg at 6 months in the RD group was as impressive as in the Symplicity HTN-1 trial. Nevertheless, in both trials (Symplicity HTN-1 and HTN-2) approximately 10% of patients had systolic blood pressure reductions <10 mmHg and were deemed nonresponders [13,14]. Importantly, RD may have additional beneficial effects on conditions other than resistant hypertension. A couple of recently published studies indicate that the benefits of RD may extend to other diseases that have a common underlying thread of elevated sympathetic activity, such as arrhythmias, left ventricular hypertrophy, heart failure, diabetes, renal failure and sleep apnea [15-17]. In addition, RD has the potential to be cost effective, particularly when performed in younger patients [18].

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The results of the Symplicity trial program are certainly encouraging. However, is RD ready for broad clinical application? While procedural and technological challenges, such as procedure time, peri-interventional pain management and vascular access, are already being addressed, several uncertainties have to be considered. The first is obviously the small number of patients and the lack of long-term follow-up data. There are concerns about the durability of the effects of the RD procedure and about potential side effects that have not been seen yet, such as impairment of renal function or latent damage to the renal artery. Since the intraluminal application of radiofrequency energy induces fibrosis of the arterial wall, it cannot be ruled out that the resulting vessel fragility could lead to stenosis or aneurysm of the renal artery 5 or 10 years later. Regarding patient selection, it would be very important to identify parameters that predict response to RD. Finally, most available data refer to reductions in office blood pressure rather than in ambulatory blood pressure. However, is office blood pressure the right parameter to assess our patients? It is common knowledge that blood pressure levels show large spontaneous intraindividual

variations. Therefore, it is essential to obtain multiple measurements taken on separate occasions over a specific period of time [4]. Ambulatory blood pressure monitoring over a 24-h period provides a blood pressure profile outside the doctor’s office and can offer additional information, such as white coat hypertension, masked hypertension, intermittent hypotension or enhanced blood pressure variability. In addition, long-term studies showed a stronger predictive value of ambulatory blood pressure monitoring for cardiovascular morbidity and mortality than office blood pressure [19]. In Symplicity HTN-1, only 27% of patients and in Symplicity HTN-2 only 40% of patients had ambulatory blood pressure measurements taken. Although systolic blood pressure levels derived from 24-h ambulatory blood pressure monitoring changed in parallel with office-based systolic blood pressure levels, the reduction was less pronounced (-11 mmHg on average).

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Since effective control of blood pressure levels in hypertensive patients is associated with a marked reduction in cardiovascular mortality and morbidity, there is a definite clinical need for adjunct therapy options in the subset of patients with resistant hypertension [6]. In our opinion, endovascular RD is an innovative and promising therapy. Thousands of patients have already been treated with RD and experience derived from clinical registries will certainly improve this therapy in the future. In the meantime, basic and translational studies will further expand our knowledge about the underlying pathophysiologic mechanisms.

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