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Review Article

Renal denervation

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ABSTRACT

Purpose of review: Renal denervation (RDN) has, within recent years, been suggested as a novel treatment option for patients with resistant hypertension. This review summarizes the current knowledge on this procedure as well as limitations and questions that remain to be answered.
Recent findings: The Symplicity HTN-1 (2009) and HTN-2 (2010) studies re-introduced an old treatment approach for resistant hypertension and showed that catheter-based RDN was feasible and resulted in substantial blood pressure (BP) reductions. However, they also raised questions of durability of BP reduction, correct patient selection, anatomical and physiological effects of RDN as well as possible beneficial effects on other diseases with increased sympathetic activity. The long awaited Symplicity HTN-3 (2014) results illustrated that the RDN group and the sham-group had similar reductions in BP.
Summary: Initial studies demonstrated that RDN in patients with resistant hypertension was both feasible and safe and indicated that RDN may lead to impressive reductions in BP. However, recent controlled studies question the BP lowering effect of RDN treatment. Large-scale registry data still supports the favorable BP reducing effect of RDN. We suggest that, in the near future, RDN should not be performed outside clinical studies. The degree of denervation between individual operators and between different catheters and techniques used should be clarified. The major challenge ahead is to identify which patients could benefit from RDN, to clarify the lack of an immediate procedural success parameter, and to establish further documentation of overall effect of treatment such as long-term cardiovascular morbidity and mortality.

1. Introduction

The relationship between the sympathetic nervous system and cardiovascular disease has long been known and, through the years, the link between increased activity in the sympathetic nervous system and resistant hypertension has been examined [1–5]. Catheter-based renal sympathetic denervation (RDN) for resistant hypertension received great attention when the safety and proof-of-principle study [6] was published in 2009 showing a marked blood pressure (BP) lowering effect and only few complications. One year later, the randomized, but unblinded Symplicity HTN-2 study [7] demonstrated very promising results. Thereafter, RDN was implemented at rapid pace, with up to 20,000 procedures performed in Europe in less than 4 years [8]. Since then, several minor studies [9–13] have supported the original observations and generated great enthusiasm. They have, however, also raised questions on the durability of BP reduction, correct patient selection, morphological and physiological effects of RDN [14–16]. It has also been suggested that the treatment may have beneficial effects in other diseases (e.g. heart failure [17], chronic kidney disease [18], sleep apnea [12,19] and arrhythmia diseases [20,21]) with increased sympathetic activity. There was, however, a need for confirmation of the original observations in a larger scaled and blinded study. This was met by the Symplicity HTN-3 study [22], which was a prospective, randomized (2:1) sham vs. procedure, single-blinded study. Surprisingly, the study showed that both the RDN group and the sham-procedure group had significant, but similar decrease in BP (Fig. 1). It is therefore questioned whether RDN treatment is indeed effective, not to mention cost effective, or whether it should be stopped awaiting results of further studies. In this article we aim to give a critical overview of RDN with main focus on its potential antihypertensive effect, but also on possible beneficial BP independent effects, including slowing the progression of chronic kidney disease (CKD), improving glucose metabolism, increasing insulin sensitivity, improving heart failure and reducing cardiac arrhythmia.

The randomized studies, and therefore mainly the Symplicity studies, will serve as the main benchmarks for RDN.

Abbreviations: BP, blood pressure; RDN, renal sympathetic denervation

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2. Medical treatment of hypertension

An effective antihypertensive treatment reduces end-organ damage related to hypertension. Treatment regimen of hypertension targets the multiple mechanisms responsible for BP elevation, such as volume overload (diuretics and aldosterone antagonists), sympathetic over activity (β-blockers and centrally acting agents) and vascular resistance (inhibition of renin–angiotensin system with angiotensin converting enzyme inhibitors or angiotensin receptor antagonists, or promotion of smooth muscle cell relaxation with calcium channel blockers or α-blockers) [23]. There are several guidelines on the treatment of hypertension [24,25]. Little data from trials are available to guide the choice of antihypertensive regimen for patients whose blood pressure remains high in spite of several medications. Recommendations are based merely on physiological principles and the clinical experience.

3. Resistant hypertension

Resistant hypertension is defined by the American Heart Association as BP that remains above a defined goal in spite of the concurrent use of 3 antihypertensive agents of different classes, ideally one of which should be a diuretic, all in optimal doses, or office BP at target BP on ≥4 antihypertensive medications [26]. The definition in itself does not distinguish between true resistant and pseudo-resistant hypertension. However, it covers overall the group of patients with apparent resistant hypertension [27]. The exact prevalence of apparent resistant hypertension is unknown, but estimated to be around 12% [28–30]. In a large retrospective cohort study of patients on 3 antihypertensive drugs at baseline – both with controlled (25.4%) and uncontrolled (74.6%) BP – 16.2% were classified as having resistant hypertension at 1 year follow-up [31]. The cardiovascular risk in patients with resistant hypertension is markedly higher than in patients with controlled hypertension [31]. Patients with resistant hypertension are characterized by older age, higher baseline systolic BP, obesity, left ventricular hypertrophy, excessive dietary salt intake, diabetes, black race and female sex [26,32]. True resistant hypertension can be diagnosed with verification by 24-hour ambulatory BP measurement (ABPM) and exclusion of secondary hypertension. A major problem and key candidate of bias in the early unblinded studies of RDN is the issue of adherence to antihypertensive medication [27]. At this point, there is undoubtedly an unmet medical need to improve BP control in these patients.

4. Pathophysiological, anatomical, and historical background of renal denervation

4.1. Pathophysiological aspects of renal denervation

Renal sympathetic nerves, both afferent and efferent (Fig. 2), are of importance for the initiation and maintenance of hypertension [2,3,33,34].

The physiologic background for RDN is based on the sympathetic activation causing increased renal vascular resistance, renin release and tubular sodium re-absorption which is present in hypertensive patients [34–36]. Several studies in animal models have shown that renal sympathectomy leads to significant reductions in BP and hypertensive end-organ-damage [2,3], and this was one of the key arguments behind testing the potential effects of RDN.

4.2. Anatomical aspects of renal denervation

The first anatomical illustration of the sympathetic nervous system dates back to 1664 where it was presented by Willis [37]. The distribution of peri-arterial sympathetic nerves in the human renal arteries is still relatively poorly understood. However, a recent study [38] of 20 human autopsy subjects (12 hypertensive and 8 non-hypertensive) have shown: 1) the number of sympathetic nerves in the proximal and middle segments of the renal artery was similar, whereas the distal segment showed fewer nerves, 2) the mean distance from nerve-to-arterial lumen was the longest in proximal segments (3.40 ± 0.78 mm) and least in distal segments (2.60 ± 0.77 mm), 3) the number of nerves was almost twice as high in the ventral region of the artery as the dorsal region. Efferent nerve fibers increase with decreasing

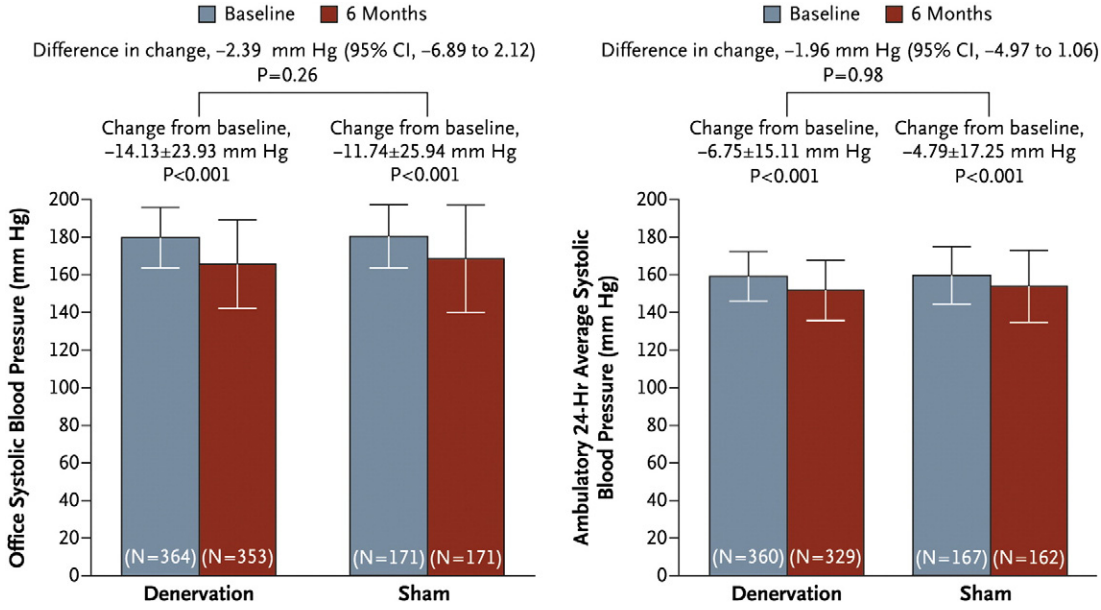

Fig. 1. Overview of the results of Symplicity HTN-3. The figure illustrates the combined Fig. 1 (Primary efficacy endpoint, Office BP) and Fig. 2 (Secondary Efficacy End Point, 24-h ambulatory BP results) from the original New England Journal of Medicine publication. In renal denervation as well as sham group, separate, significant reductions are seen in primary and secondary efficacy endpoints. Compared reductions are insignificant.
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