

# Expanded indications for transcatheter renal denervation

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## Abstract

Renal denervation (RDN) is a catheter-based procedure introduced in 2009 as a treatment of resistant hypertension. The method is based on the concept that resistant hypertension is a result of hyperactivity of the sympathetic nervous system (SNS), and therefore reducing the impact of the SNS by ablating the renal nerves should eliminate the condition. Since 2009 numerous investigators have proven the procedure to be safe and effective, which contributed to the quick success and wide spread of the method, subsequently triggering further research in this area. The dynamic distribution of the procedure induced investigators to examine the influence of RDN on other conditions involving hyperactivity of the SNS (such as atrial fibrillation or ventricular arrhythmia). A few studies aiming to explain the influence of RDN on arrhythmias in patients with resistant hypertension have been conducted. The results in treating atrial fibrillation additionally to pulmonary vein ablation and electrical storm appear to be promising; however, the data are limited and further investigations need to be done. The influence of RDN on insulin resistance, left ventricular hypertrophy and heart failure are possible. Perspectives of expanding indications are discussed. Renal denervation appears to be a promising way of treating hypertension and raises hope for a wider group of patients with conditions closely related to hyperactivity of the sympathetic nervous system such as arrhythmia.

**Key words:** renal denervation, atrial fibrillation, ventricular arrhythmia.

## Introduction

Renal denervation (RDN) is a catheter-based procedure introduced in 2009 as a treatment of resistant hypertension. The method is based on the concept that resistant hypertension is a result of hyperactivity of the sympathetic nervous system (SNS), and therefore reducing the impact of the SNS by ablating the renal nerves should eliminate the condition. Since 2009 numerous investigators have proven the procedure to be safe and effective, which contributed to the quick success and wide spread of the method, subsequently triggering further research in this area. The dynamic distribution of the procedure induced investigators to examine the influence of RDN on other conditions involving hyperactivity of the SNS (such as atrial fibrillation or ventricular arrhythmia).

## The safety and efficiency of the procedure investigated in two prospective registries, Simplicity HTN-1 and Simplicity HTN-2

In Simplicity HTN-1 [1] a cohort of 45 patients with resistant hypertension was examined. The average baseline office blood pressure equalled 177/101 (mean 4.7 antihypertensive

medications). After the procedure the office blood pressure decreased significantly by  $-14/-10$ ,  $-21/-10$ ,  $-22/-11$ ,  $-24/-11$ , and  $-27/-17$  mm Hg at respectively 1, 3, 6, 9, and 12 months. The mean reduction in noradrenalin spillover was 47%. During the procedure one case of renal artery dissection was noted (prior to the delivery of radiofrequency energy); no other renovascular complications occurred.

The longer-term follow-up data of 153 patients (including the 45 patients examined in the previous study) have been published [2]. The study group included 31% diabetic patients and 22% patients with coronary heart disease; the mean age was 57. The baseline office blood pressure equalled 176/98 (mean 5.1 antihypertensive drugs). The decrease in office blood pressure was 23/11 mm Hg ( $n = 130$ ); 26/14 mm Hg ( $n = 107$ ); 32/14 mm Hg ( $n = 59$ ), at 12, 18, 24 months, respectively. In 92% of patients a reduction in the blood pressure by  $\geq 10$  mm Hg was observed. In 97% of patients (149/153) there were no complications, in 3 patients groin pseudoaneurysm occurred, in 1 patient renal artery dissection was noted.

In Simplicity HTN-2 106 eligible subjects were randomised 1 : 1 to either immediate RDN or to a control group [3]. The primary end point was the change in the office blood pres-

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sure measured at 6 months follow-up. At this point control group patients become eligible to receive the treatment. Office blood pressure in the RDN group 6 months after the procedure declined from 178/98 by 32/12 mm Hg (compared with no significant change in the control group).

### Further direction of research, expanding indications

The presence of hypertension is commonly associated with increased sympathetic activity. Catheter-based renal denervation, which impairs afferent and efferent sympathetic nerves, has been shown to effectively reduce blood pressure. The positive effects of the procedure on resistant hypertension, as well as proven whole-body norepinephrine spillover reduction, provoked a search for new indications for the procedure.

### Supraventricular arrhythmias

Positive effects of RDN were anticipated also regarding supraventricular arrhythmias. Hypertension is one of the major risk factors for atrial fibrillation (AF). Moreover, the incidence of AF increases with left ventricle hypertrophy, coronary heart diseases, and heart failure [4, 5], all being the consequences of poorly controlled hypertension. Recent studies have shown that changes in autonomic nervous system activity may have an impact on the remodelling process due to AF [6, 7]. Linz *et al.* described the effect of RDN on a patient with permanent AF [8]. In 1-year follow-up a reduction of ventricular heart rate and blood pressure was observed. Further studies conducted on pig models for AF revealed a reduction in the heart rate during sinus rhythm (RR interval, 708 ±12 vs. 577 ±19 s;  $p = 0.0021$ ), increased atrioventricular node conduction duration (PQ interval, 112 ±12 ms vs. 88 ±9 ms;  $p = 0.0001$ ) and a reduction in ventricular rate during AF episodes by 24% (119 ±9 vs. 158 ±19 bpm;  $p = 0.0001$ ). Modulation of the atrial effective refractory period or AF-induced atrial electrical remodelling was not observed. It should however be emphasized that studies on pig models provide only assessment of short-term results of the procedure.

In other studies Pokushalov *et al.* [9] investigated the impact of renal denervation on patients with refractory symptomatic AF, referred for pulmonary vein isolation (PVI). The research showed that RDN resulted in a reduction of blood pressure, both systolic (from 181 ±7 to 156 ±5,  $p < 0.0001$ ) and diastolic (from 97 ±6 to 87 ±4,  $p < 0.0001$ ) in 1-year follow-up and reduced AF recurrences when performed with PVI.

Modulation of autonomic nervous system activity obtained by the RDN procedure may provide better control of ventricular heart rhythm in patients with AF and also decrease susceptibility for AF but further investigation is required. All those data suggest that block of both afferent and efferent sympathetic nerves is more effective than elimination of efferent cardiac nerves only.

### Ventricular arrhythmia

The sympathetic nervous system plays an important role in the onset, maintenance and termination of ventricular arrhythmia [10]. Most typically sympathetic activation enhances ventricular arrhythmia while vagal tone suppresses its occurrence. The onset of ventricular arrhythmias is provoked by shortening the effective ventricular refractory time, being a result of sympathetic stimulation [11]. That is the background for the theory that modulating the activity of the autonomic nervous system might suppress the incidence of ventricular arrhythmias directly and consequently decrease the risk of sudden cardiac death [12].

### Electrical storm

Activation of the sympathetic nervous system plays a significant role in triggering cardiac arrhythmias, and thus may be considered as a possible target for renal artery denervation. In 2011 Ukena *et al.* [13] first reported the potential role of RDN in treatment of electrical storm as first-in-man experience. He described 2 patients with symptomatic heart failure (NYHA class III) who suffered from recurrent episodes of ventricular arrhythmias.

The first RDN procedure was performed on a 67-year-old male patient with hypertrophic cardiomyopathy admitted with cardiogenic shock due to electrical storm. Later studies revealed multiple forms of monomorphic ventricular tachycardia (VT). Before admission the patient underwent several endo- and epicardial radiofrequency ablation procedures. Despite taking maximum doses of antiarrhythmic drugs episodes of monomorphic VT were noted. After the RDN procedure the patient continued event-free up to 5 months after RDN. On further follow-up 2 episodes of VTs were noted due to transient hypokalaemia (2.8 mM), which after correction did not recur.

The second patient was a 57-year old man with idiopathic dilated cardiomyopathy and severely reduced systolic LV function (EF 28%). He also suffered from permanent atrial fibrillation and type 2 diabetes mellitus on intensive insulin therapy. He presented recurrent episodes of polymorphic VT or ventricular fibrillation. After declining cardiac ablation he underwent an RDN procedure. Within the next 24 h 12 episodes of VF occurred, but during the next 6 months no ventricular tachyarrhythmias were recorded. Moreover, the patient could systematically reduce insulin doses and finally terminate the medication.

In both cases, RDN did not affect blood pressure in comparison to values observed before the procedures, which may indicate that RDN causes reduction of blood pressure only if it is elevated due to increased sympathetic activity.

### Left ventricular hypertrophy

Left ventricular hypertrophy (LVH) has been linked with the occurrence of arrhythmias and an increased cardiovascular mortality rate. Like hypertension it is often a result

of persistent SNS hyperactivation [14]; therefore reducing the impact of the SNS might lead to decreased incidence of arrhythmia. A study investigating the influence of RDN on LVH has recently been published [15]. Forty-six patients underwent the procedure, and 18 patients served as a control group. Six months after the procedure the left ventricle (LV) mass index was reduced from 112.4 g/m<sup>2</sup> to 94.9 g/m<sup>2</sup> ( $p = 0.004$ ) in the RD group, while in the control group no significant change was obtained.

## Heart failure

Ventricular arrhythmias are often a result of structural heart disease that leads to heart failure. That is the reason for common co-occurrence of ventricular arrhythmias and heart failure. A first-in-man experience concerning RDN in patients with hypertension and heart failure has been published [16]. After 4 weeks of follow-up the blood pressure had been reduced; no complications were noted.

## Conclusions

Catheter-based renal denervation has been shown to be a considerably safe and effective method of treating resistant hypertension. The sympathetic nervous system has a pathophysiological role not only in hypertension but also in conditions that are comorbid with it. That was a trigger factor for experimental and clinical studies, searching for other positive effects of RDN. A few studies aiming to explain the influence of RDN on arrhythmias in patients with resistant hypertension have been conducted. The results appear to be promising, although the data are limited and further investigations need to be done. There is also a need of data explaining the effect of the procedure on patients without hypertension, presenting arrhythmias only. It is well known that videoscopic left sympathetic cardiac denervation is highly effective in adrenergic arrhythmias in patients with long QT syndrome and catecholaminergic polymorphic ventricular tachycardia [17]. Renal denervation as a less invasive method could be a promising alternative treatment for these patients.

To conclude, RDN appears to be a promising way of treating hypertension and raises hope for a wider group of patients with conditions closely related to hyperactivity of the sympathetic nervous system such as arrhythmia. However, we are still lacking data involving larger groups of patients and investigation on patients with arrhythmia solely.

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