Expert review

Renal denervation – current evidence and perspectives

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A b s t r a c t

Clinical trials have demonstrated that catheter-based renal denervation (RDN) reduces blood pressure and improves blood pressure control in patients with resistant hypertension. The follow-up data indicate that the blood pressure lowering effect of the procedure may last for up to 36 months. Despite the fact that RDN is a growing and promising technique, still more data from clinical trials are needed to support the long-term safety and persistent efficacy of this approach as compared to the best possible pharmacological treatment. It would also be particularly important to recognize the clinical features of patients who would benefit most from RDN as well as the clinical characteristics of non-responders to the procedure. As renal denervation also reduces whole-body sympathetic nerve activity, the clinical entities characterized by sympathetic nervous system activation – including hypertension coexisting with metabolic abnormalities and/or sleep apnea, chronic kidney disease, heart failure, and arrhythmias – may be potential new indications for the procedure. However, only a few small clinical studies so far have shown the potential benefit of renal denervation in these clinical situations and large clinical trials are needed to prove this concept. Catheter-based RDN is a promising (but also novel) therapeutic approach and further studies should also verify whether it can be considered as a procedure in management of patients not only with resistant hypertension, but also as a tool in the treatment of mild to moderate forms of hypertension.

Key words: renal denervation, resistant hypertension, hypertension.

Introduction

Being one of the most frequent chronic diseases worldwide, arterial hypertension remains a global health problem. Despite significant progress in diagnosis and pharmacological treatment, still too few patients with hypertension are treated effectively. One of the challenging issues in the management of hypertension is resistant hypertension, which is usually defined as a failure to reach the blood pressure (BP) goal in patients adhering to adequate doses of an appropriate 3-drug regimen including a diuretic [1]. The prevalence of resistant hypertension in the overall hypertensive population ranges from 5% to 30% depending on the population examined and the scope of screening methods; however, a figure less than 10% probably represents the true incidence [1–5]. Resistant hypertension is an important clinical problem due to the relatively high prevalence in the population of hypertensive patients, the associated increased risk of cardiovascular and renal events, as well as more pronounced organ damage as compared to patients with well-controlled arterial hypertension [1–7]. This clinical entity undoubtedly requires proper diagnostic strategies and effective therapeutic interventions. Until recently treatment options for patients with resistant hypertension were limited to non-invasive therapeutic strategies – lifestyle changes and pharmacological treatment [7–10]. In the multi-factorial etiology of resistant hypertension, the crucial role of the sympathetic nervous system have been particularly postulated [11, 12]. This resulted in a new approach targeting the renal sympathetic nerves – catheter-based renal denervation (RDN), which has become a developing therapy option in the management of patients with resistant arterial hypertension [1, 8–10].

The pathophysiological background

The role of sympathetic renal nerves in the development and course of hypertension has been proven in both animal experimental models and in human studies [13, 14]. There are two types of sympathetic renal nerves – renal afferent nerves and renal efferent nerves, creating a neural network within the adventitia of the renal artery. The afferent sympathetic fibers originate from the kidneys, and by modulating central sympathetic outflow they directly modify neurogenic hypertension. The acti-

vation of efferent nerves enhances sodium and water retention, stimulates renin release and alters renal blood flow [12–14]. In this way, renal sympathetic nerves influence short- and long-term BP control [8]. In the 1930s surgical sympathectomy was introduced with good clinical effect [15]. However, because of numerous side effects – including orthostatic hypotension, tachycardia, bladder, bowel and erectile dysfunctions – as well as high perioperative mortality and complication rate, this method was finally abandoned. Nevertheless, at the beginning of the twenty first century, the convenient location of both afferent and efferent sympathetic renal nerves adjacent to the adventitia of renal arteries enabled an endovascular approach and selective, minimally invasive renal denervation. After confirming the efficacy and safety of this method in animal studies, the first human trials were conducted.

Percutaneous renal denervation (RDN) is performed via the renal artery lumen, using a 5 Fr Symplicity catheter (Symplicity™ Catheter System, Ardian/Medtronic Inc., California, USA – the first denervation system used in humans), connected to a radio-frequency (RF) generator. After local anesthesia and a routine femoral approach, the catheter is advanced into the distal part of the renal artery trunk (proximally to the bifurcation) through a 6 Fr guiding catheter inserted into the renal artery ostium. Then, discrete, low-powered (5–8 W), up to 2-minutes lasting RF ablations are applied. Sequential catheter retraction and rotation enables achievement of up to 4–8 ablations separated longitudinally and rotationally within the trunk of each renal artery. Catheter-tip impedance and temperature are constantly recorded and energy delivery is performed according to the predefined algorithm. Before the procedure unfractionated heparin is administered to maintain adequate anticoagulation (activated clotting time above 250 s), whereas analgesics and sedatives manage the visceral abdominal pain accompanying the procedure. Bilateral percutaneous renal denervation can be accomplished in ca. 40 min to 60 min.

Beside the first renal denervation system used – Medtronic's Symplicity system – others are currently available, including St. Jude's EnligHTN™ system, Boston Scientific's Vessix™ system, Covidien's One Shot™ system, Recor's Paradise™ and Cardiosonic's TIVUS™ system [8]. In the last two systems an ultrasound beam instead of radiofrequency current energy is delivered.

Clinical studies – efficacy and safety

The results of an initial "proof of concept" trial was published in Lancet in 2009 [16]. A total of 50 patients with systolic blood pressure (BP) ≥ 160 mm Hg despite concurrent use of 3 or more antihypertensive drugs (including diuretics) were included in the study. The procedure was performed in 45 patients with renal arter-

ies anatomically suitable for the treatment (the trunk at least 4 mm in diameter and 20 mm in length) and not meeting the following exclusion criteria: an estimated glomerular filtration rate (eGFR) below 45 ml/min per 1.73 m^2, type 1 diabetes mellitus, renovascular abnormalities (including multiple main renal arteries, previous angioplasty and hemodynamically significant renal artery stenosis) or a known secondary cause of hypertension other than sleep apnea or chronic kidney disease. The RDN resulted in significant reduction of systolic/diastolic BP after 1, 3, 6, and 12 months (–14/–10, –21/–10, –22/–11, –27/–17 mm Hg, respectively). A substantial degree of efferent nerve denervation, consistent with BP response, was confirmed by the observation of a decline of 47% in total norepinephrine outflow from the kidney into circulation (norepinephrine spillover) assessed in a subgroup of 10 patients. Regarding the safety of the procedure, two adverse events not directly related to energy application were reported (1 renal artery dissection, 1 femoral artery pseudoaneurysm). The imaging test repeated 1 and 6 months after the procedure did not show any substantial abnormalities such as renal artery stenosis or aneurysm. The "proof of concept" Symplicity-HTN-1 trial demonstrating the safety and initial efficacy of the procedure led to design of the first randomized trial Symplicity-HTN-2 [17]. Similar inclusion and exclusion criteria, except for diuretic treatment necessity, were established and 106 patients were enrolled. Baseline blood pressure was 178/96 mm Hg, despite treatment with 5.3 antihypertensive drugs on average. Patients were randomly assigned to the RDN (52 patients) or control group (54 patients). Six months after RDN a significant reduction of the office BP (–32/–12 mm Hg) was achieved as compared to no changes in the control group. The follow-up data were obtained from 49 patients and 51 controls. In 84% of patients a systolic BP reduction of at least 10 mm Hg was achieved and no reduction was observed in only 10% of the treated group. In 20 patients 24-hour BP recordings were assessed – the reduction in BP after 6 months was –11/–7 mm Hg with minor changes (–3/–7 mm Hg) in the control group. Similarly, the BP in home self-measurements decreased in treated patients by –20/–12 mm Hg in comparison to a mild increase of 2/0 mm Hg in the controls.

In 2011, long-term follow-up data of the extended group of 153 patients (including the initial cohort of 45 patients from the "proof of concept" study) treated with RDN in a non-randomized manner were reported as Symplicity-HTN-1 trial results [18]. Baseline BP was 176/98 mm Hg, despite treatment with a mean of 5 antihypertensive medications. Postprocedural office BPs were reduced by –20/–10, –24/–11, –25/–11, –23/–11, –26/–14, and –32/–14 mm Hg at 1, 3, 6, 12, 18, and 24 months, respectively. The presented 36-month long-term follow-up of this non-randomized

small study confirmed a sustained BP-lowering effect of 33/19 mm Hg [19]. The durability of the therapeutic effect of RDN is therefore confirmed by the findings of this study, with a sustained BP reduction up to 3 years after the procedure. The sustained reduction in BP during the long-term follow-up period suggests no nerve regrowth or functional recovery as well as no development of counter-regulatory BP elevating mechanisms, which is of considerable clinical and pathophysiological relevance [19].

The Simplicity trials demonstrated that RDN reduces office BP in patients with resistant hypertension. However, only limited data on the effect of the procedure on 24-hour ambulatory BP were available from Symplicity-HTN-2, in which only 20 patients were assessed according to ambulatory BP monitoring (ABPM) [17]. As certain concerns about the effects of RDN on 24-hour BP have been raised [20], Mahfoud *et al.* conducted a study in which they assessed the ambulatory BP changes after RDN in patients with resistant hypertension [21]. The study included 303 patients with true resistant hypertension (office SBP 172.2 ±22 mm Hg; 24-hour SBP 154 ±16.2 mm Hg) and 43 with pseudoresistant hypertension (office SBP 161.2 ±20.3 mm Hg; 24-hour SBP 121.1 ±19.6 mm Hg). At 3, 6, and 12 months follow-up office SBP and DBP were significantly reduced in both groups of patients, while only in patients with true resistant hypertension was a significant reduction in 24-hour BP demonstrated. In patients with true resistant hypertension a significant reduction was, therefore, observed in 24-hour SBP (–10.1/–10.2/–11.7 mm Hg, $p < 0.001$), diastolic BP (–4.8/–4.9/–7.4 mm Hg, $p < 0.001$), maximum SBP (–11.7/–10.0/–6.1 mm Hg, $p < 0.001$) and minimum SBP (–6.0/–9.4/–13.1 mm Hg, $p < 0.001$) at 3, 6, and 12 months, respectively. This recent study demonstrates that RDN reduces office BP, but also decreases 24-hour BP values measured by ABPM in patients with true resistant hypertension.

The largest, prospective, randomized, masked procedure single-blind trial – Symplicity HTN-3 – with eligibility criteria similar to those used in previous symplicity trials, but including a sham treatment, started on September 2011 (clinicaltrials.gov identifier: NCT01418261). The study was designed to enroll 530 patients with uncontrolled hypertension in US sites and the first results will be available in the spring of 2014 [22].

An open label, multi-indication registry – the Global Simplicity Registry (GSR) – is also currently being conducted worldwide to evaluate the safety and efficacy of treatment with the Symplicity RDN system in 5000 uncontrolled hypertensive patients. Over 1000 patients have been enrolled in the GSR so far. The early results from 3, 6, 12-months follow-up were presented at the ESC Congress 2013 by Böhm and support the concept that RDN is both an effective and a safe procedure in reducing BP.

The acute procedural complications reported in both Symplicity Trials (HTN-1 and HTN-2, 209 procedures) included 4 groin pseudoaneurysms (treated with manual compression), 1 renal artery dissection managed with stent implantation without further complications, one urinary tract infection, one postprocedural drop in BP resulting in a reduction in antihypertensive drugs, and one extended hospitalization for assessment of paresthesia. Vasovagal reactions occurred in 22 patients (10.5%) during the intervention and they were sufficiently managed with atropine. It is noteworthy that 3 of 4 groin complications that occurred in patients treated with a first generation Symplicity catheter required an 8 Fr introducer sheath. Long-term side effects included transient dizziness (6 patients), pitting edema (3 patients) and bilateral flank pain (4 patients). In the 124 patients with 6-month non-invasive imaging data, no irregularities or new stenoses at any treatment site were found. Two patients had progression of a preexisting renal artery stenosis, one required no therapy and the other one was successfully stented. The location of both stenoses was quite distant from the sites of RF energy delivery, suggesting no relationship to the RDN. Two patients died within the follow-up period due to cardiovascular events. Neither death was considered by the study investigator or Data Safety Monitoring Board to be attributable to the device or the procedure.

There have been certain concerns about the possible negative influence of that RDN on renal function [20]. In the Symplicity HTN-1 trial with an extended follow-up of 24 months in 64 patients, estimated glomerular filtration rate (eGFR) remained stable during the first year of follow-up. However, only in 10 patients are eGFR data of the 2-year follow-up currently available. In this group of 10 patients a reduction of 16 ml/min/m^2 was observed and it was explained as possibly related to changes in therapy with diuretics [18]. Mahfoud *et al.* investigated the effect of RDN on renal function and urinary albumin excretion in 100 patients with resistant hypertension and preserved renal function. At 6 months follow-up no adverse effects on eGFR or renal structure were observed, while a reduced number of patients with micro- and macroalbuminuria was noted [23]. It is noteworthy that one of the exclusion criteria in the Symplicity trial was an eGFR of less than 45 ml/min/1.73 m^2, due to safety concerns. The preliminary data on RDN in patients with moderate-to-severe chronic kidney disease showed that the procedure is effective and safe in the studied population [24], also indicating that these patients should only be treated in clinical studies with subsequent follow-ups.

Other studies have assessed the effect of RDN on the physiological response during cardiopulmonary exercise [25] and the occurrence of orthostatic hypertension [26]. Renal denervation was found not to cause chronotropic incompetence during exercise or alteration in the orthostatic response [25, 26].

Patient selection based on current recommendations

Patients in whom treatment with RDN is considered should meet certain criteria. According to available evidence [16–18], patients are eligible for RDN if they have treatment-resistant hypertension defined as office SBP ≥ 160 mm Hg (≥ 150 mm Hg in type 2 diabetes) despite concurrent use of at least three antihypertensive drugs in adequate doses, including a diuretic. The resistance of hypertension in office BP measurements should be confirmed in ABPM; thereby pseudo-resistance has to be excluded. According to the Expert consensus document from the European Society of Cardiology on catheter-based renal denervation [8], each patient considered for RDN should have been evaluated by a hypertension expert in specialized centers (e.g. Hypertension Excellence Centers). It is well known that resistant hypertension may originate from certain lifestyle factors such as obesity or large weight gains, excessive alcohol consumption and high sodium intake; therefore in patients with resistant hypertension, lifestyle modification always has to be implemented. Before considering RDN, a patient with resistant hypertension should also necessarily be screened for secondary causes of hypertension including primary hyperaldosteronism, renal artery stenosis and

pheochromocytoma. Optimization of antihypertensive drug treatment should be part of the work-up; however, it is noteworthy that an attempt of treatment with mineralocorticoid receptor antagonists is not a necessary condition before consideration of RDN [1, 8].

For safety reasons it is also postulated to implement the following exclusion criteria based on those used in the Symplicity trials [16–18]: previous renal artery intervention (balloon angioplasty or stenting), evidence of renal artery atherosclerosis (defined as renal artery stenosis over 50%), presence of multiple main renal arteries in either kidneys or main renal arteries of < 4 mm in diameter or < 20 mm in length. Despite the preliminary data [24] proving the safety and effectiveness of renal denervation in patients with moderate-to-severe chronic kidney disease, in patients considered for RDN the kidney function should be preserved (GFR ≥ 45 ml/min per 1.73 m²).

The current criteria for RDN are summarized in Table 1.

New potential indications for renal denervation

Patients with hypertension and glucose metabolism alterations

Activation of the sympathetic nervous systems contributes to insulin resistance [27], is associated with cen-

Table 1. Criteria patients should meet before RDN is considered [1, 8–10]

	ESC Expert Consensus [8]	ESH Position Paper[10]	Polish Expert Consensus [9]	ESH/ESC Guidelines [1]
Office SBP	≥ 160 mm Hg (in type 2 diabetes ≥ 150 mm Hg)	≥ 160 mm Hg (in type 2 diabetes ≥ 150 mm Hg)	≥ 160 mm Hg	≥ 160 mm Hg
Office DBP	*	*	*	≥ 110 mm Hg
Exclusion of pseudoresistance	Yes (in ABPM average BP > 130 mm Hg or mean daytime BP > 135 mm Hg)	Yes (using ABPM and home BP monitoring)	Yes (using ABPM)	Yes (using ABPM)
Antihypertensive regimen	≥ 3 antihypertensive drugs in adequate dosage and combination (incl. diuretic)	≥ 3 (better ≥ 4) antihypertensive drugs in adequate dosage and combination (incl. diuretic)	≥ 3 antihypertensive drugs in adequate dosage and combination (incl. diuretic)	≥ 3 antihypertensive drugs in adequate dosage and combination (incl. diuretic)
Necessity of MRA in drug regimen	No	Yes (if clinically possible)	*	No
eGFR	≥ 45 ml/min/1.73 m²	≥ 45 ml/min/1.73 m²	≥ 45 ml/min/1.73 m²	*
Anatomy of renal arteries	– No polar or accessory arteries – No renal artery stenosis – No prior revascularization	– Main renal artery diameter ≥ 4 mm – main renal artery length ≥ 20 mm – No multiple renal arteries – No significant renal artery stenosis – No prior revascularization	– Main renal artery diameter ≥ 4 mm – No significant renal artery stenosis – No renal artery aneurysm – No prior revascularization	*
Lifestyle modification	Yes	Yes	Yes	Yes
Exclusion of secondary hypertension	Yes	Yes	Yes	Yes

*BP – blood pressure, ABPM – ambulatory blood pressure monitoring, GFR – glomerular filtration rate, MRA – mineralocorticoid receptor antagonists, *not specified*

tral obesity [28], and increases the risk of diabetes mellitus [29] and metabolic syndrome [30]. The results from a pilot study indicate that RDN can have a favorable influence on glucose metabolism [31]. Fifty patients with resistant hypertension were included in the study and 37 of them underwent RDN. In the treatment group a significant BP reduction was accompanied by substantial glucose and insulin concentration decrease and improvement in insulin sensitivity.

Two patients with polycystic ovary syndrome underwent RDN and were evaluated 3 months after the procedure. The preliminary report of these two cases suggests that RDN not only reduces blood pressure, but also improves insulin resistance in the absence of changes in body weight [32].

Patients with hypertension and obstructive sleep apnea

We evaluated the effects of RDN on blood pressure and sleep apnea severity in 10 patients with resistant hypertension and sleep apnea. At 6 months, a decrease in apnea-hypopnea index in polysomnography was noted. Interestingly, significant decreases were also observed in plasma glucose concentration 2 h after glucose administration and in hemoglobin A_{1c} level [33]. A prospective, randomized, open-label trial assessing the effects of renal denervation on blood pressure and clinical course of obstructive sleep apnea and glucose metabolism in patients with resistant hypertension is currently being conducted in the Institute of Cardiology in Warsaw (clinicaltrials.gov identifier NCT01366625). The study is designed to enroll 60 patients with resistant hypertension coexisting with sleep apnea.

Heart failure

It is well known that cardiovascular morbidity and mortality in patients with chronic heart failure are significantly reduced by β-blockers – agents that act antagonistically to the sympathetic nervous system. As increased sympathetic activity in patients with chronic heart disease has prognostic significance, RDN may be considered as being potentially beneficial in this group of patients.

The effects of RDN on cardiac function and left ventricular hypertrophy have already been investigated in one study [34]. In 46 patients with resistant hypertension, beyond substantial BP lowering, a significant reduction in left ventricular mass and mean interventricular septum thickness, as well as improvement of diastolic function (assessed by mitral valve lateral E/E') and improvement of ejection fraction, were demonstrated. A small first-in-man pilot study including 7 normotensive patients with chronic heart failure was conducted [35]. At 6 months follow-up a substantial improvement of the patients' 6-min walk distance and the self-assessment of patients' comfort was observed, whereas there were no changes in BP or

renal function, and no symptomatic fluctuations in hemodynamics were noted. These preliminary data led to the design of a randomized, controlled, multi-centre, currently ongoing trial (RE-ADAPT-HF) that investigates the effects of renal denervation in 100 patients with chronic heart failure (NYHA functional class II–III). Another multicentre, randomized controlled trial was designed to evaluate renal denervation as a treatment option for heart failure with normal left ventricular ejection fraction (HFNEF) in 60 patients (DIASTOLE trial) [36]. These first big trials investigating patients with chronic heart failure will undoubtedly provide important information on the role of RDN in this group of patients.

Arrhythmias

The impact of RDN on arrhythmias was investigated in ventricular tachyarrhythmias (2 cases) [37] and refractory atrial fibrillation (AF) (13 patients) [38]. In a first-in-human experience renal denervation was used as bailout therapy in two patients with congestive heart failure suffering from treatment-resistant electrical storm. In both patients ventricular tachyarrhythmias were significantly reduced after performing RDN. In a study investigating the impact of RDN in patients with refractory AF and resistant hypertension, 27 patients were randomly assigned to pulmonary vein ablation alone (14 patients) or pulmonary vein ablation plus renal denervation (13 patients). At follow-up a significant reduction in BP and significantly fewer episodes of AF were observed in the pulmonary vein ablation plus renal denervation group. Nevertheless, to establish the role of RDN in the field of arrhythmias, further investigation on a larger number of patients is needed.

Renal failure

Sympathetic activation in chronic kidney disease may contribute to development of hypertension and progressive decline in renal function. For safety reasons in Simplicity HTN trials, patients with eGFR < 45 ml/min/1.73 m^2 were excluded. The preliminary study including 15 patients with moderate-to-severe chronic kidney disease demonstrated a significant blood pressure lowering effect of RDN with no further decline in GFR or effective renal plasma flow 6 months after the procedure in this group of patients [24]. Nevertheless, because of limited data, patients with higher grades of renal failure should only undergo RDN in the context of clinical research studies which will establish the role of this procedure in this group of patients [8].

Summary

According to current ESH/ESC Guidelines for the management of arterial hypertension, in patients with resistant hypertension RDN may be considered in case of ineffectiveness of drug treatment (IIb/C) [1]. In patients with

resistant hypertension whose BP cannot be controlled by a combination of lifestyle modification and pharmacological treatment, screening for secondary causes of hypertension has to be conducted and pseudoresistance has to be excluded before considering RDN. According to the Expert consensus document of the European Society of Cardiology on catheter-based renal denervation, each patient considered for renal denervation should have been evaluated by a hypertension expert in specialized centers [8].

The clinical trials demonstrated that catheter-based RDN reduces BP and improves BP control in patients with resistant hypertension. The follow-up data available show that the BP lowering effect of the procedure may last for up to 36 months. Nevertheless, we are still waiting for results of the largest, prospective, randomized, masked procedure single-blind trial – Symplicity-HTN-3 – which will bring us the most objective answer on the role of RDN in the management of patients with resistant hypertension [22].

Although RDN is a growing and promising technique, more data are still needed to prove the long-term safety and persistent efficacy of this approach versus the best possible pharmacological treatment. It would also be particularly important to recognize the clinical features of patients who would benefit the most from RDN as well as the clinical characteristics of non-responders to the procedure.

As RDN reduces whole-body sympathetic nerve activity, the clinical entities characterized by sympathetic nervous system activation – including hypertension coexisting with metabolic abnormalities and/or sleep apnea, chronic kidney disease, heart failure, and arrhythmias – may be the potential new indications for the procedure. However, there has been no strong evidence for these clinical situations and large clinical trials are needed to prove this concept.

Catheter-based RDN is a promising but also novel therapeutic approach and further research should verify whether it can be considered as a procedure in management of patients not only with resistant hypertension, but also as a tool in the treatment of mild to moderate forms of hypertension.

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Disclosures

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