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CURRENT OPINION

Expert consensus document from the European Society of Cardiology on catheter-based renal denervation†

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Introduction

Hypertension is highly prevalent and one of the most frequent chronic diseases worldwide.[1] It has been suggested that over the next two decades up to 50% of the adult population will be diagnosed with hypertension, according to the standard guideline definitions.[1] Despite the availability of many safe and effective antihypertensive drugs, control rates to target blood pressure remain low.[2] Approximately 5–10% of all patients with high blood pressure are resistant to drug treatment defined as blood pressure >140/90 mmHg, >130–139/80–85 mmHg in diabetes mellitus or >130/80 mmHg in chronic kidney disease in the presence of three or more antihypertensives of different classes, including a diuretic, at maximal or the highest tolerated dose.[3] Resistant hypertension is associated with an increased risk of cardiovascular events.[4] Current non-invasive therapeutic strategies are mainly based on lifestyle interventions and pharmacological treatment, including mineralocorticoid receptor antagonists.[3] Up until recently treatment options for patients with resistant hypertension were limited. Nowadays catheter-based renal denervation offers a new approach targeting the renal sympathetic nerves. Indeed, the technique has been shown to reduce sympathetic nerve activity,[5] norepinephrine spillover[6] as well as blood pressure[7–9] in patients with resistant hypertension. Several national[10–13] and international[14] consensus documents from different societies have recently been published, with different degrees of involvement of interventionalists. This expert consensus document summarizes the view of an expert panel of the European Society of Cardiology and the European Association of Percutaneous Cardiovascular Interventions to provide guidance regarding appropriate patient selection, efficacy, safety, limitations, and potential new indications of renal denervation for referring physicians, interventionalists, and healthcare providers.

Pathophysiology

The aetiology of resistant hypertension is multi-factorial. However, there is a large body of evidence indicating the crucial role of the sympathetic nervous system in most types of hypertension and numerous

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cardiovascular diseases, including heart failure, chronic kidney disease, and the metabolic syndrome.[15,16] Afferent and efferent sensory, chemo- and baroreceptor nerve fibres, form a neural network within the adventitia of the renal artery (*Figure 1*).[17] Renal afferent nerves connect the kidney with the hypothalamus, and are activated by renal ischaemia and high local adenosine concentrations.[18] Renal afferent nerve traffic contributes to central sympathetic activity generated in the solitary tract and nucleus. Efferent nerves innervate the renal vasculature, the tubular segment of the nephron, and juxtaglomerular renin-containing granular cells, enhancing sodium and water retention, stimulating renin release, and altering renal blood flow.[16] These effects influence both short- and long-term blood pressure regulation. Their convenient location in the renal artery adventitia means that both the efferent and afferent fibres can now be targeted by catheter-based approaches, thereby re-setting renal blood pressure regulation. Catheter-based radiofrequency ablation has been shown to be as effective as surgical denervation in terms of reducing kidney norepinephrine content in pigs (*Figure 2*).[19]

The procedure

Numerous new percutaneous renal nerve ablation systems are currently being tested and will soon be released into the market. Up to now, five Conformité Européenne-marked renal denervation systems using different treatment strategies are available: Medtronic's Symplicity system, St. Jude's EnligHTN system, Vessix's V2 system, Covidien's One Shot system, and Recor's Paradise system (for details, see *Table 1*). Most of these systems use radiofrequency energy to target renal sympathetic nerves except for the ultrasound-based Recor's Paradise system. The devices are all inserted percutaneously via a femoral access and advanced under fluoroscopic control. Beforehand, however, renal artery anatomical suitability for the procedure should be established, i.e. a renal artery length is ideally >20 mm with a diameter of >4 mm. When considering renal nerve ablation, arteries with visible stenosis, with calcification or atheromatous plaques, represent relative contraindications. Anectodical reports of renal denervation in arteries with significant stenosis (>50%) or previous revascularization have been reported, but this off-label use should be avoided. Recently published data indicated that the applied radiofrequency energy resulted in transient local de-endothelialization, acute cellular swelling, connective tissue coagulation, and thrombus formation.[20] Although controlled data are lacking, these observations suggest that the use of antiplatelet therapy during the procedure (acetylsalicylic acid 250 mg i.v.) and for up to 4 weeks after renal denervation (75–100 mg/day p.o.) might be advisable.

Owing to the co-location of sympathetic nerves and C pain fibres, analgesia and sedation (e.g. using midazolam, morphine, remifentanile, fentanyl, or propofol) is mandatory during radiofrequency ablation. The presence of an anaesthesiologist is not generally necessary, however, in some countries required. During the procedure vital signs (including blood pressure, heart rate, and oxygen saturation) need to be monitored. In some patients, radiofrequency ablation may causes renal artery oedema and/or spasm at the treatment sites, which can be treated by using intra-arterial nitroglycerine or verapamil. Even when vascular spasm is persistent during the procedure despite these treatments it typically disappears within hours after the ablation. The procedural time normally ranges from 45 to 60 min.

Numerous new catheter systems and treatment modalities for renal denervation are under development. The products include new radiofrequency catheters, but also novel treatment modalities using catheter-based ultrasound energy, cryoablation techniques,

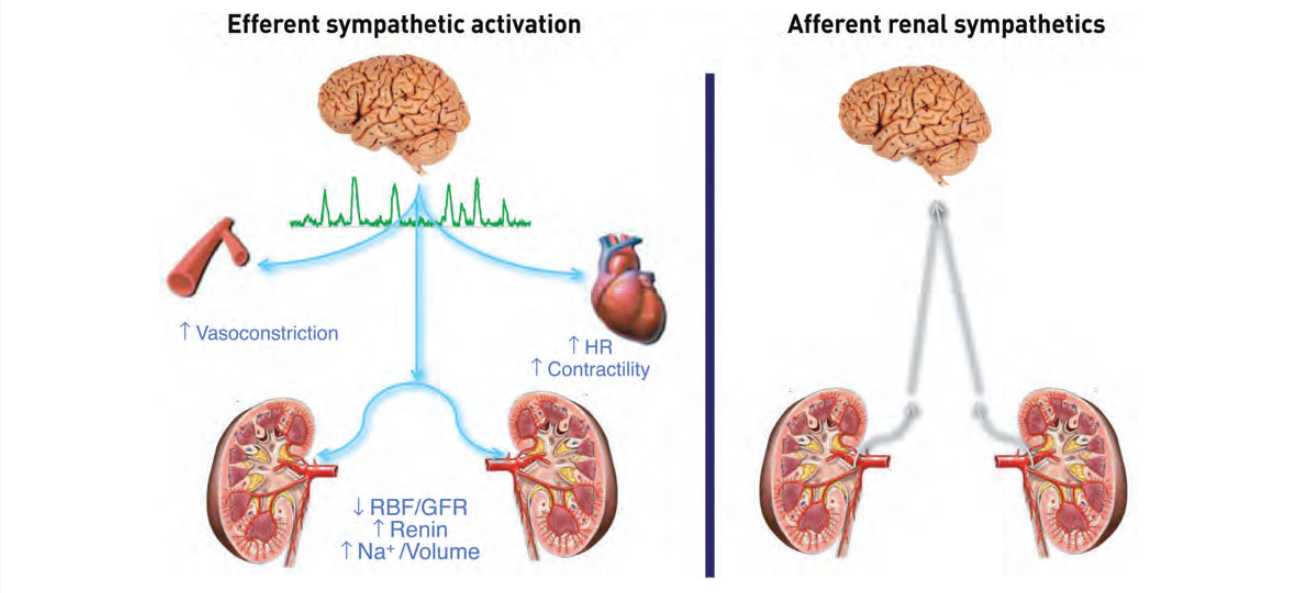

Figure 1 Efferent and afferent renal sympathetic nerves (modified with permission from Lüscher, PCR-EAPCI Textbook). HR, heart rate; RBF, renal blood flow; GFR, glomerular filtration rate.

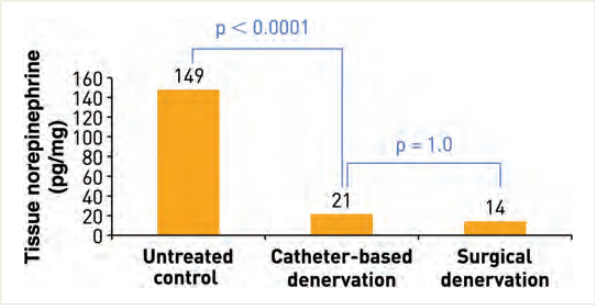

Figure 2 Tissue norepinephrine content in untreated controls and pigs undergoing catheter-based renal denervation and surgical denervation (modified from[19]).

radiation, local drug-delivery, or even external application of ultrasound energy. It is important to note that all the new devices presented above and especially those using new treatment modalities such as ultrasound or chemical denervation will have to show favourable safety and efficacy profiles in a larger cohort of patients with subsequent long-term follow-up before a general use can be recommended.[21]

Clinical trials

Efficacy

The initial proof-of-concept study Symplicity HTN-1[6] and the multi-centre, prospective, randomized Symplicity HTN-2 trial[7] investigated the effect of renal denervation in 45 and 106 patients with resistant hypertension, respectively. Baseline blood pressure was 177/100 and 178/96 mmHg, respectively, despite treatment with four or more antihypertensive drugs on average. Renal denervation resulted in significant systolic and diastolic blood pressure reductions that were first observed at 1 month (−14/−10 mmHg, $P = 0.026$) and persisted out to 24 months (−32/−14 mmHg, $P = 0.001$).[8] The presented 36-month long-term follow-up of this non-randomized small study confirmed a sustained blood pressure-lowering effect of 33 and 19 mmHg ($P < 0.01$, $n = 34$).[22] Self-measured home blood pressure assessed in a subgroup of 32 patients decreased by 20/12 mmHg ($P < 0.0001$), compared with 2/0 mmHg in 40 control patients. As expected, the reduction in ambulatory blood pressure monitoring over 24 h after renal denervation was smaller compared with the observed changes in office-based blood pressure (i.e. 11/7 mmHg; $P = 0.007$, $n = 20$). The response to treatment was defined as a reduction in systolic blood pressure (SBP) >10 mmHg at 6-month follow-up and was found in 84% of patients.

It is important to note that blood pressure rarely changes immediately after the procedure. It often takes several weeks to months before a notable blood pressure reduction occurs, suggesting that a slowly progressive resetting of sympathetic neural regulation occurs. Patients and treating physicians should therefore be informed to avoid unrealistic expectations in the immediate aftermath of the procedure. Furthermore, it is important to communicate to patients and referring physicians that renal denervation as currently deployed

Table 1 Details of the five CE-marked renal denervation devices

Catheter system	French	Energy	Electrodes/ polarity	Design	Patients[a]	Longest follow-up[a]	BP changes at 6 months (mmHg)[a]	BP changes at longest follow-up (index a)	Study
Symplicity	6F	RF	1 unipolar	Single-tip	235	36 months ($n = 34$)	−32/−12 ($n = 49$)	−33/−16 ($n = 34$)	Symplicity HTN-1,[22] HTN-2[7,9] (NCT00888433, NCT00664638)
EnligHTN	8F	RF	4 unipolar	Basket	46	6 months ($n = 45$)	−26/−10 ($n = 45$)	−26/−10 ($n = 45$)	EnligHTN-1[23] (NCT01438229)
Vessix V2	8F	RF	4–8 bipolar	Over-the-wire balloon	10	1 month ($n = 10$)		−30/−10 ($n = 10$)	REDUCE-HTN (NCT01541865)[b]
OneShot	7/8F	RF	1 unipolar	helical, irrigated balloon	9	1 month ($n = 9$)		−31/−6 ($n = 9$)	RHAS[58]
Paradise	7/8F	Ultrasound	1 transducer	fluid-filled balloon	15	12 months ($n = 3$)	−32/−17 ($n = 11$)	−25/−13 ($n = 3$)	REDUCE[59]

F, French; BP, blood pressure; RF, radiofrequency.
[a]Data are referring to manuscript published or orally presented.
[b]Hoppe UC, oral presentation during EuroPCR 2012, Paris, France.

is designed to improve blood pressure control in patients whose blood pressure is resistant to control with conventional drug therapy. In this regard, renal denervation is unlikely to significantly reduce pill burden in most patients and is not a cure for hypertension. Neither in the Symplicity HTN-1 nor in the HTN-2 a reduction in antihypertensive background medication has been investigated as an endpoint. Of note, both studies have been sponsored by the manufactures of the renal denervation device (Ardian/Medtronic).

Safety

In the Simplicity trials, the treatment was performed without major complications in 98% (201 of 209) of the cases included.[6–8] The following complications have been reported: three femoral artery pseudoaneurysms, one urinary tract infection, one case of back pain, one extended hospitalization for assessment of paresthaesia, and one renal artery dissection during placement of the guiding catheter. Vasovagal reactions occurred in seven patients (13%) during the intervention, which resolved under treatment with atropine. Six-month renal vascular imaging in 130 patients who underwent renal denervation identified one patient with possible progression of an underlying atherosclerotic lesion, which required no therapy. Two case reports have been published describing a secondary rise in blood pressure after renal denervation caused by a progression of a renal artery stenosis.[24,25] It remains unanswered to which extent the ablation procedure and/or the catheter manipulation induced or promoted the rapid development of renal artery stenosis or whether it represented a natural progression of the disease process.

Concerns have been raised that renal denervation might negatively influence renal function.[26] In the Symplicity HTN-1 trial with an extended follow-up of 24 months in 64 patients, estimated glomerular filtration rate (eGFR) (measured by modification of diet in renal disease) remained stable during the first year of follow-up, whereas eGFR data of the 2-year follow-up is currently available only in 10 patients.[8] In these 10 patients, eGFR was reduced by 16 mL/min/1.73 m^2, which was thought to be related to changes in diuretic therapy. The effect of renal denervation on renal function and urinary albumin excretion has been investigated in 100 patients with resistant hypertension and preserved renal function.[27] The study demonstrated a reduced number of patients with micro- and macroalbuminuria after renal denervation, without adversely affecting glomerular filtration rate (GFR) or renal artery structure within 6 months. It is important to note that, in the Symplicity trials, patients with an eGFR of <45 mL/min/1.73 m^2 were excluded as a matter of safety. Although preliminary data suggest that renal denervation is also safe and effective in patients with moderate-to-severe chronic kidney disease,[28] these patients should only be treated in clinical studies with subsequent follow-ups.

The effect of renal denervation on the physiological response during cardiopulmonary exercise testing has been tested.[29] Renal denervation resulted in a significant drop in resting, maximum exercise, and recovery blood pressure, whereas heart rate response during exercise and oxygen uptake was well preserved.

Another concern has been the occurrence of orthostatic hypotension after renal nerve ablation as it has occurred in the 1950's with surgical sympathectomy for severe hypertension.[30] Fortunately, such a side-effect does not seem to occur with catheter-based renal denervation; indeed, a recent study investigated blood pressure changes upon changes in posture without evidence for an alteration in the orthostatic response after the procedure.[31]

Limitations

One of the major challenges is how to monitor the success of the procedure. There are no easily deployed tests to determine whether the denervation procedure has been wholly or partially effective or ineffective. Furthermore, not all patients respond to treatment with blood pressure lowering. Is this because there is a hypertensive phenotype that is destined not to respond to the procedure or, that the procedure has not been deployed effectively in these patients? Thus, parameters predicting the likelihood of response and the overall success of the renal denervation procedure are lacking. However, as in trials of antihypertensive drugs, SBP at baseline has been identified as one predictor of the magnitude of the BP-lowering response,[27] which might be at least in part explained by the statistical phenomenon of 'regression to the mean'. In Symplicity HTN-2,[7] an intake of centrally acting sympatholytics was identified as a predictor of pronounced blood pressure response, which is surprising because one might have expected drugs targeting the same mechanism as renal denervation to be more effective. At present, no negative blood pressure predictors have been identified and as noted above there are no reliable biochemical or other parameters, suitable for everyday clinical practice, for assessing the success of renal denervation or the degree of renal denervation achieved.

The exact mechanisms by which renal denervation results in a blood pressure reduction are not yet fully established, but are likely to include a reduction in total peripheral resistance, reduced renin release, and favourable alterations of water and salt handling. Of note, measurements of sympathetic nerve traffic in the peroneal nerve revealed that sympathetic activity is also reduced after renal denervation.[5] This is important because it suggests that whole-body sympathetic nerve activity is reduced following the procedure, most likely due to reduced afferent central nervous system input directing a reduction in central sympathetic outflow.[5] However, one published study reported in a small group of 12 patients no significant overall blood pressure-lowering effect and no changes in muscle sympathetic nerve activity after renal denervation (RDN).[32] The interpretation of this study is limited to the fact that, in contrast to the Symplicity trials, the baseline BP was only 157/85 mmHg (thereby $\approx$20/10 mmHg lower) and some of the subjects had non-treatment-resistant hypertension (42% of the patients had SBP $\leq$140 mmHg).[33] Thus, lower blood pressure responses had to be expected although sympathetic activation is present even in mild forms of hypertension.[34] Differently, in a larger case-controlled series of patients, all with confirmed multi-drug-resistant hypertension and elevated blood pressure report a mild reduction of multi-unit muscle sympathetic nerve activity (MSNA) and a significant reduction in single-fibre MSNA was reported.[5] The series differ in both entry blood pressure and multi-unit MSNA bursts/100 heart beats, and underlying pharmaceutical use.

Whether the effects of renal denervation will be sustained beyond the time span currently documented (36 months)[22] is uncertain. Indeed, animal studies and transplant experiments have demonstrated that sympathetic renal nerves have the capacity to re-grow

and/or regenerate over time.[35–37] Therefore, the long-term efficacy of the procedure still remains an important question, because only limited information about the long-term follow-up of patients is available, both in clinical trails and in real-life setting. The available 36-month follow-up data of the Symplicity HTN-1 trial[22] are encouraging as they show a sustained blood pressure-lowering effect, suggesting a significant and functionally relevant regrowth of the renal nerves is unlikely. The question whether a repeated intervention with RDN could be performed in patients with inadequate response to a first procedure has been raised. However, with present knowledge, this could not be recommended.

Only limited information about the impact of renal denervation on daytime, night-time, and average blood pressure is available from the Symplicity HTN-2 trial[7] and from that data it has been argued that renal denervation might not reduce ambulatory blood pressure equally as effectively as office blood pressure.[26] A multi-centre analysis of more than 300 patients undergoing renal denervation has subsequently shown that the procedure significantly reduces office and 24 h average, daytime, and night-time blood pressure in patients with resistant hypertension and increases the percentage of patients controlled to target blood pressure values, both according to office blood pressure and ambulatory blood pressure monitoring (Mahfoud F, Homburg/Saar, data on file).

In contrast to some antihypertensive drug regimen, renal denervation has not been shown to affect cardiovascular morbidity and mortality. Although outcome improvement is very likely, when a strong blood pressure reduction is accepted as a valid outcome surrogate in severe and resistant hypertension, this clearly represents an unmet need and has to be investigated in future trials to definitely determine the role of this device-based therapy. The multi-centre, prospective, single-blinded, randomized, placebo-controlled Symplicity HTN-3 study (NCT01418261) is recruiting patients in the USA, which will hopefully answer the question of whether a contributing placebo effect imposes bias on the results of renal denervation.

Patient selection

According to the available evidence,[6–8] patients are eligible for renal denervation if they have (severe) treatment-resistant hypertension defined by office SBP ≥160 mmHg (≥150 mmHg in type 2 diabetes) despite treatment with at least three antihypertensive drugs of different types in adequate doses, including one diuretic. In certain centres, uncontrolled blood pressure values >140/90 mmHg are taken as reference. High office blood pressures should be confirmed by ambulatory blood pressure monitoring and pseudo-resistance has to be excluded. Pseudo-resistant hypertension should be considered particularly in patients whose clinical blood pressure is consistently higher than out-of-office measurements (mean daytime BP < 135 mmHg).[38] Before a patient with uncontrolled hypertension is considered for renal denervation, patients should have been evaluated by a hypertension expert in specialized centres (e.g. Hypertension Excellence Centers; see http://www.eshonline.org/Communities/CentresList.aspx). Optimization of antihypertensive drug treatment and identification of contributing lifestyle factors should be part of the work-up. Special emphasis should be put on the potential additional advantages of the treatment with mineralocorticoid receptor antagonists (i.e. spironolactone, eplerenone), which may be particularly effective in patients with resistant hypertension.[39] However, concerns have been raised about the long-term safety of these drugs especially in patients with reduced renal function and already existing blockade of the renin–angiotensin system.[14] Therefore, a general recommendation that only patients in whom treatment with mineralocorticoid receptor antagonists has failed, should be considered for renal denervation, cannot be sustained. Secondary hypertension, including renal artery stenosis, pheochromocytoma, sleep apnoea syndrome, and primary hyperaldosteronism, must be systematically ruled out. *Figure 3* summarizes the recommended screening process before a patient is considered for renal denervation. Based on the exclusion criteria of the Symplicity trials,[6–8] the following criteria should also be implemented in order to safely proceed to renal denervation: previous renal artery intervention (balloon angioplasty or stenting), evidence of renal artery atherosclerosis (defined as a renal artery stenosis >50%), presence of multiple main renal arteries in either kidneys or main renal arteries of <4 mm in diameter or <20 mm in

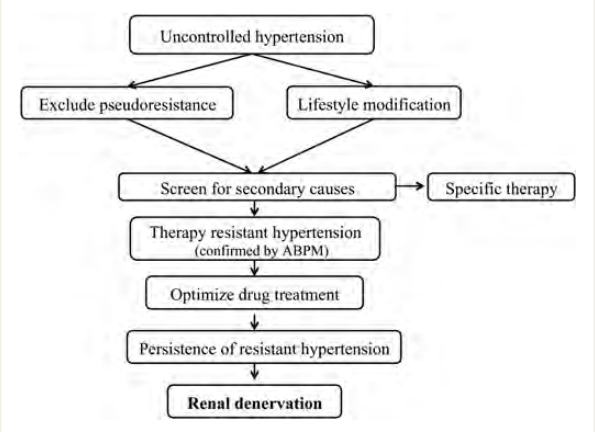

Figure 3 Appropriate screening is mandatory to select the right patients (modified from[57]).

Table 2 Criteria patients should comply with before renal denervation is considered

- Office-based systolic BP ≥ 160 mmHg (≥150 mmHg diabetes type 2)
- ≥3 antihypertensive drugs in adequate dosage and combination (incl. diuretic)
- Lifestyle modification
- Exclusion of secondary hypertension
- Exclusion of pseudo-resistance using ABPM (average BP > 130 mmHg or mean daytime BP > 135 mmHg)
- Preserved renal function (GFR ≥45 ml/min/1.73 m^2)
- Eligible renal arteries: no polar or accessory arteries, no renal artery stenosis, no prior revascularization

BP, blood pressure; ABPM, ambulatory blood pressure monitoring; GFR, glomerular filtration rate.

length. The kidney function should be preserved (GFR ≥45 mL/min per 1.73 m^2), although renal denervation seems to be safe and effective also in patients with moderate-to-severe chronic kidney disease.[28] *Table 2* summarizes the criteria for renal denervation according to the currently available clinical evidence. It should also be considered that patients presenting with resistant hypertension often report adverse effects of antihypertensive therapy. So far, no study has been published to investigate the effect of renal denervation in patients intolerant to various drugs, although this can be a relevant problem. Therefore, no general recommendation can be given at this time. However, in patients with reproducible drug intolerance or significant adverse effects an individualized decision-making process appears to be reasonable.

Centre selection

In patients with uncontrolled hypertension, secondary causes of hypertension are common. Therefore, a detailed screening process is mandatory to identify patients with potentially curable forms of hypertension, since renal denervation is not an effective therapy in these patients. Centres should be specialized in the management of hypertension (e.g. Hypertension Excellence Centers, see http://www.eshonline.org/Communities/CentresList.aspx), with at least one hypertension expert being actively involved in the treatment and screening process. In order to avoid high complication rates, it is recommended that the interventions are performed by interventional cardiologists or angiologists who have been trained in performing this specific intervention and who are qualified to manage potential complications, such as acute dissection of renal arteries by stent implantation. Appropriate expertise could be assumed in centres with >25 renal interventions per year. At this stage of the introduction of the procedure, centres should enter their data into large registries to ensure proper quality control and to allow for an analysis of the procedural success acutely and at long-term follow-up. *Table 3* provides suggested follow-up examinations after renal denervation.

Cost-effectiveness

The cost-effectiveness and long-term clinical benefits of renal denervation in patients with resistant hypertension have recently been published,[40] using a state-transition (Markov) model. The results indicate that renal denervation, although the treatment represents an additional cost at the time of the procedure (hospitalization, catheter, and operator costs), appears to offer a great value over time and might be cost-effective when compared with other medical treatments. The estimated incremental lifetime cost-effectiveness ratio was $3071 per quality-adjusted life-year and thereby below the commonly accepted threshold of $5000. Predicted median survival was 18.4 years for renal denervation and 17.1 years for standard of care. However, these assumptions will be sensitive to costs in different healthcare systems and are based on the assumption that blood pressure-lowering drugs or denervation offer no value or harm beyond their impact on blood pressure lowering.

Potential beneficial effects beyond blood pressure lowering

Diabetes mellitus and insulin resistance

Activation of the sympathetic nervous system is a main contributor to insulin resistance, metabolic syndrome, associated with central obesity, and risk of developing diabetes.[41,42] A bidirectional relationship between sympathetic overactivity inducing insulin resistance and hyperinsulinemia producing sympathetic activation exists. In a pilot

Table 3 Suggested follow-up examinations after renal denervation

	Baseline	3 months	6 months	12 months	24 months	36 months	48 months	60 months
Office BP	X	X	X	X	X	X	X	X
ABPM	X	X	X	X	X	X	X	X
Heart rate	X	X	X	X	X	X	X	X
Body weight	X	X	X	X	X	X	X	X
Review medications	X	X	X	X	X	X	X	X
Blood tests, including GFR determination	X	X	X	X	X	X	X	X
ECG	X		X	X	X	X	X	X
Renal artery imaging (duplex ultrasound, MRI/CT with contrast or angiogram)	X		X	X	X	X	X	X
Oral glucose tolerance test (where appropriate)	X		X	X	X	X	X	X
Echocardiography in patients with heart failure or left ventricular hypertrophy	X		X	X	X	X	X	X
UACR in patients with albuminuria	X	X	X	X	X	X	X	X

BP, blood pressure; ABPM, ambulatory blood pressure monitoring; ECG, electrocardiogram; UACR, urine albumin to creatinine ratio.

study[43] renal denervation positively influenced glucose metabolism in patients with resistant hypertension. Three months after the procedure fasting glucose, fasting insulin and 2 h glucose concentration during oral glucose tolerance testing were significantly reduced resulting in a significant improvement of insulin sensitivity (measured using the HOMA index), whereas there were no changes in the control group. Similar findings have been reported from a study,[44] investigating the effect of renal denervation in patients with obstructive sleep apnoea. Beside reductions in the severity of obstructive sleep apnoea, the authors report changes in 2 h glucose concentration during oral glucose tolerance test and reductions in HbA1c. A preliminary report in two patients with polycystic ovary syndrome[45] suggests that renal denervation lowers blood pressure and improves insulin resistance (measured by euglycemic clamp technique) in the absence of changes in body weight over a 3 month period. Further trials are necessary to document the durability of these results as well as their implications for the management of patients with diabetes.

Cardiac effects

Neurohumoral activation, in particular activation of the sympathetic nervous system, is of prognostic relevance in patients with chronic heart failure and antagonism of the sympathetic system with beta-blockers significantly reduces cardiovascular morbidity and mortality.[46] The kidneys have been identified as a main contributor to the complex pathophysiology, formally called cardiorenal syndrome.[47] One published study[48] investigated the effects of renal denervation on left ventricular mass and diastolic filling pattern in 46 patients with resistant hypertension in which renal denervation was associated with substantial reductions in blood pressure and significantly reduced left ventricular mass and mean interventricular septum thickness. Diastolic function (as assessed by mitral valve lateral E/E′) was improved after renal denervation and there was a reduction of left ventricular filling pressures and improvement in ejection fraction. In a small first-in man pilot study, involving seven normotensive patients with chronic heart failure, 6 months after renal denervation, their 6 min walk distance improved significantly and the patients' self-assessment of well-being also improved.[49] There were no significant changes in blood pressure, renal function, and no symptomatic fluctuations in haemodynamics. A randomized, controlled multi-centre trial (RE-ADAPT-CHF) investigating the effects of renal denervation in 100 patients with chronic heart failure (NYHA functional class II–III) is currently underway and will provide important information.

Chronic kidney disease

Abundant evidence shows that chronic kidney disease is characterized by sympathetic activation, contributing to hypertension and the progressive loss of renal function.[50] Renal denervation could therefore be a potentially novel therapeutic strategy in patients with impaired renal function, including end-stage kidney disease. However, in the Symplicity HTN trials, patients with GFR <45 mL/min/1.73 m^2 were excluded, thus, because the safety of such an intervention in this patient population is uncertain. Recently, the effects of renal denervation in a small series of 15 patients with moderate-to-severe chronic kidney disease (mean GFR 31 mL/min/1.73 m^2) were reported.[28] Renal denervation was effective in terms of blood pressure lowering and there was no evidence of a further decline in GFR or effective renal plasma flow 6 months after the procedure, despite exposure to contrast medium. Owing to the limited data, however, patients with higher grades of renal insufficiency should only be treated in the context of clinical research studies.

Antiarrhythmic effects

The autonomic nervous system also modulates cardiac electrophysiology properties including chronotropy and dromotropy, depolarization rate of the sinus node, and atrioventricular conduction.[51] Renal denervation has been shown to significantly reduce the resting heart rate in patients with resistant hypertension and prolonged PR interval.[52] Interestingly, neither baseline heart rate nor changes in heart rate correlated with the blood pressure reductions. 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.[53] Following renal denervation, ventricular tachyarrhythmias were significantly reduced in both patients. The impact of renal denervation in patients with refractory atrial fibrillation and resistant hypertension has been assessed in a study.[54] Twenty-seven patients were randomized to pulmonary vein isolation alone or pulmonary vein isolation plus renal denervation. Besides significant reductions in blood pressure, patients in the pulmonary vein isolation plus renal denervation group experienced significantly fewer episodes of atrial fibrillation at follow-up. Furthermore, animal experiments support the antiarrhythmic effects of renal denervation and suggest a reduced inducibility of atrial fibrillation after the procedure.[55] Thus, the role of renal denervation in the field of arrhythmias deserves further exploration in well-defined research protocols. However, due to the limited number of patients investigated so far, a routine use cannot be recommended.

Hypertensive end-organ damage

It has been shown that pulse wave reflection and augmented pulse wave velocity representing vascular stiffness are adversely related to cardiovascular morbidity and mortality in patients with hypertension. Renal denervation significantly reduced central pulse pressure, associated with peripheral pulse pressure, and resulted in a reduction of pulse wave velocity indicating vascular peripheral re-remodelling effects.[56] This was especially documented in patients with high vascular stiffness at baseline. Albuminuria has been extensively investigated to be a sign of early renal damage in hypertension and can be regarded as hypertensive end-organ damage. It has been shown that renal denervation could reduce the number of patients with macroalbuminuria and microalbuminuria to lower grades of urinary albumin excretion resulting in a higher portion of individuals without micro- or macroalbuminuria during follow-up of 6 months.[27]

Summary

Current evidence from the available clinical trials strongly support the notion that catheter-based radiofrequency ablation of renal nerves reduces blood pressure and improves blood pressure control in patients with drug-treated resistant hypertension, with data now extending out to 36 months. Accordingly, renal

denervation can be considered as a therapeutic option in patients with resistant hypertension, whose blood pressure cannot be controlled by a combination of lifestyle modification and pharmacological therapy according to current guidelines. The fact that renal denervation also reduces whole-body sympathetic nerve activity suggests that this therapy may also be beneficial in other clinical states characterized by sympathetic nervous system activation—this may ultimately lead to new indications.

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