



Catheter-based renal denervation for treatment of resistant hypertension

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Summary

Hypertension is a common disease associated with important cardiovascular complications. Persistent blood pressure of 140/90 or higher despite combined use of a renin–angiotensin system blocker, calcium channel blocker and a diuretic at highest tolerated doses constitutes resistant hypertension. Excess sympathetic activity plays an important pathogenic role in resistant hypertension in addition to contributing to the development of metabolic problems, in particular diabetes. Reduction of renal sympathetic activity by percutaneous catheter-based radiofrequency ablation via the renal arteries has been shown in several studies to decrease blood pressure in patients with resistant hypertension, and importantly is largely free of significant complications. However, longer term follow-up is required to confirm both long-term safety and efficacy.

Introduction

Hypertension is a common disease that gives rise to multiple complications such as ischaemic heart disease, myocardial infarction, cerebrovascular accident, cardiac and renal failure¹. The World Health Organization's *Global status report on non-communicable diseases 2010*² states that hypertension accounts for 12.8% of all deaths each year worldwide.

The National Institute of Health and Clinical Excellence (NICE) has provided guidance for health professionals in order to achieve the best outcome in management of hypertension in the UK. Blood pressure reading of systolic 140 mmHg and diastolic 90 mmHg or above with ambulatory blood pressure reading of 135/85 or higher defines hypertension. Hypertension can be said to be resistant to pharmacological therapy if the blood pressure remains 140/90 or higher despite combined use of a renin–angiotensin

system blocker, calcium channel blocker and a diuretic all at optimal doses.³The 7th report by the Joint National Committee⁴ on prevention, detection, evaluation and treatment of high blood pressure also uses the same definitions for hypertension and resistant hypertension. There are several other organizations in different parts of the world that provide guidelines about diagnosis and management of hypertension such as the European Society of Hypertension,⁵ The American Society of Hypertension⁶ and Hypertension Canada 2013.⁷ Although they differ in specifics of hypertension staging and management, all essentially agree on the definition of resistant hypertension.

Methods

Here we have reviewed the literature on resistant hypertension and the role of renal denervation

therapy in its treatment. All relevant literature was gathered from PubMed, using the keywords 'hypertension' and 'renal denervation'.

Resistant hypertension: risk factors and secondary causes

Daugherty *et al.*⁸ reported that 2% of patients who are diagnosed with incidental hypertension develop resistant hypertension within 18 months of diagnosis, and that the risk of cardiovascular complications is 50% higher in patients with resistant hypertension. Several lifestyle factors increase the risk of developing resistant hypertension, in particular high alcohol and salt intake. In addition, renal parenchymal disease, pheochromocytoma, renal artery stenosis, primary aldosteronism, Cushing's syndrome and thyroid disease are important secondary causes of resistant hypertension that need to be screened for. However, in the majority of patients with resistant hypertension, an underlying case cannot be identified. Patients who develop resistant hypertension are at high risk of developing retinopathy, left ventricular failure and renal failure.⁹

Sympathetic nervous system and hypertension

Excess sympathetic activity in the kidneys plays an important role in the aetiology of hypertension. Afferent and efferent sympathetic nerves localized in the adventitia of the renal arteries are critical in blood pressure control. Efferent sympathetic postganglionic neurones, which are affected and regulated by central sympathetic activity and renorenal reflexes, innervate juxtaglomerular granular cells, arterioles and tubules of the kidney. Excess production of noradrenaline gives rise to spillover in the blood stream, which can be measured. The efferent sympathetic postganglionic neurones consist of different types of nerve fibres which stimulate different targets, giving rise to sodium and water retention in the body (by acting on the renal tubules), renin secretion or vasoconstriction at different levels of stimulation. On the other hand, the afferent sympathetic nerves have a sensory role communicating information from the kidney to the central sympathetic control centres which then modulate sympathetic tone

in different organs.^{10–13} In a study that was performed on 22 hypertensive and 11 normotensive subjects, the hypertensive patients were found to have increased noradrenaline spillover due to increased sympathetic nervous activity and reduced noradrenaline reuptake.¹⁴

In the context of chronic kidney disease, increased sympathetic activity has been suggested to contribute importantly to the hypertensive state seen in these patients.¹⁵ Indeed, Neumann *et al.*¹⁶ have reported a >60% increase in muscle sympathetic nerve activity, used as a measure of generalized sympathetic tone, in patients with chronic kidney disease compared with healthy controls. Hypoxic damage to the kidneys and activation of the renin–angiotensin system are suggested to activate the afferent sympathetic nerves from the kidneys, thus leading to hypertension.¹⁷

In addition to causing hypertension, increased sympathetic nervous system activity is also suggested to contribute to the development of metabolic problems, in particular diabetes.¹⁸

Studies on renal denervation

Deactivating the renal sympathetic innervation has been shown to significantly improve hypertension.¹⁹ Catheter-based renal denervation is the technique that is preferred to traditional surgical denervation, since surgical sympathetic denervation is reported to be associated with >50% mortality in addition to other serious adverse events such as postural hypotension, syncope and erectile dysfunction. On the other hand, the catheter-based renal denervation technique appears to be far safer for patients and allows for selective denervation of the target nerve.²⁰ Catheter-based renal denervation involves inserting a catheter into the renal artery, which allows introduction of one or more electrodes for radiofrequency ablation of the sympathetic nerves surrounding the renal arteries.^{21,22} Different types of device are used for catheter-based renal denervation. The Symplicity device (Medtronic Mountain View, California, USA)²³ is well known and established, and was used in the Symplicity HTN1 and Symplicity HTN2 as well as the ongoing Symplicity HTN3 trials. It uses a 6F catheter and a generator connected to an electrode which allows low-grade radiofrequency ablation to be performed in one area at a time; a series of ablations are delivered

at different positions along each renal artery, in a helical pattern, to achieve effective denervation. The EnligHTN™ multi-electrode renal denervation system (St Jude Medical St. Paul, USA)²⁴ uses four electrodes which deliver ablations at different points in the artery simultaneously; which reduces the radiofrequency ablation time, decreases the need to reposition the electrodes and allows for greater accuracy during the procedure. Covidien²⁵ have produced the OneShot device which uses a balloon-shaped catheter that allows for radiofrequency ablation of the entire wall of the artery at once. RAPID (Rapid Renal Sympathetic Denervation for Resistant Hypertension Using the OneShot Ablation System) is an ongoing trial looking at the outcome of renal denervation using Covidien's OneShot device. A different approach is that utilized by the ReCor Medical PARADISE (Percutaneous Renal Denervation System); this uses ultrasound energy that is delivered to the artery through a balloon-shaped catheter. This design allows for shorter treatment time. In addition, the catheter cools itself down while delivering the treatment which can potentially decrease the risk of damaging the arterial walls.¹³

Schlaich *et al.*²⁶ published one of the first reports which showed the effect of catheter-based renal denervation in resistant hypertension. A patient with resistant hypertension with mean blood pressure of 161/107 despite being on seven different antihypertensive drugs underwent renal denervation therapy to both of his renal arteries. This resulted in reduction in his mean blood pressure to 141/90 over the first month and to 127/81 at one year following the intervention. In addition, noradrenaline measurements after the procedure showed that noradrenaline spillover from the kidneys was significantly reduced by 48% and 75% from the left and right kidneys, respectively. Krum *et al.*²⁷ performed a safety and proof-of-principle cohort study on catheter-based renal denervation, evaluating hypertension control, safety and noradrenaline spillover following the procedure. Fifty patients with resistant hypertension who had mean blood pressures of 177/101, without any discernible secondary causes of hypertension or renal disease, were enrolled into this study. Systolic blood pressure was reduced by 27 mmHg and diastolic blood pressure by 17 mmHg over 12 months

following the procedure. In addition to achieving good blood pressure control, a reduction of 47% in noradrenaline spillover was observed. There were no important adverse effects during or after the procedure. Another similar study, Symplicity HTN-1, was carried out on a larger scale in 2011. One hundred and fifty-three patients with resistant hypertension from different parts of Europe, USA and Australia with mean blood pressure of 176/98 underwent catheter-based renal denervation. Over 24 months of follow-up, patients exhibited important reductions in blood pressure (mean reduction 32 mmHg systolic and 14 mmHg diastolic). In addition, renal function of these patients (based on estimated glomerular filtration rate) remained stable and unchanged from baseline during the 24 months of follow-up. Although overall the procedure was found to be safe, complications such as minor flank pain, renal artery dissection and pseudoaneurysms were identified in a small number of patients.²⁸ Symplicity HTN-2 studied the effect of catheter-based renal denervation in patients with resistant hypertension who had systolic blood pressure ≥ 160 mmHg in 24 centres in different parts of Europe, New Zealand and Australia. Out of the 106 patients who took part in the study, 52 patients were treated with catheter-based renal denervation in addition to continuing their antihypertensive medications and 52 patients continued with usual pharmacological treatment. The six-month follow-up results showed that the group who underwent renal denervation exhibited a large and significant reduction in blood pressure (mean reduction of 32/12 mmHg), whereas the control group did not. In addition to confirming the beneficial role of catheter-based renal denervation in treatment of resistant hypertension, the Symplicity HTN-2 trial, similar to the other studies mentioned above, revealed no important complications due to the procedure.²⁹ Forty-six of the subjects in the control group also underwent renal denervation after the six-month follow-up period was over. One-year follow-up results since the beginning of Symplicity HTN-2 have shown similar results to those at six months, with continued reduction in blood pressure both in subjects who underwent renal denervation at the beginning of the study and in the crossover group. In addition, no major adverse events were noted at one-year follow-up.³⁰

Several studies have also suggested that patients with resistant hypertension undergoing renal denervation may experience beneficial effects on other coexistent chronic conditions. One study has shown that patients with stage 3 and stage 4 chronic kidney disease undergoing the procedure experienced reduction in their blood pressure without any deterioration in renal function.³¹ The hope therefore is that renal denervation might slow down deterioration in renal function in patients with chronic kidney disease, due to its beneficial blood pressure-lowering effects and the attendant attenuation of end-organ damage,³² but this remains to be proven.

Mortensen *et al.*³³ investigated the effect of renal denervation on arterial stiffness. Twenty-one patients with resistant hypertension were treated with renal denervation, and six-month follow-up results showed that the subjects experienced significant reduction in arterial stiffness and improvement in pulse wave velocity in addition to demonstrating reduction in blood pressure.

As mentioned above, hypertension is a risk factor for cardiac problems including left ventricular hypertrophy due to increased sympathetic nervous activity. REACH (REnal Artery denervation in Chronic Heart failure) was a first-in-human study which investigated the safety and effect of renal denervation in chronic systolic heart failure. Seven patients with heart failure who were on standard medication for heart failure at highest tolerated doses and with mean blood pressure of 112/65 mmHg underwent bilateral renal denervation therapy. Six-month follow-up results showed that subjects experienced a major improvement in heart failure-related symptoms without experiencing any major adverse events or hypotensive episodes.³⁴ Brandt *et al.*³⁵ studied the effect of renal denervation on cardiac function in patients with resistant hypertension. 46 of the patients involved in the study were treated with catheter-based renal denervation and 18 control patients has usual care; all patients underwent transthoracic echocardiography at the beginning of the study, and at one and six months post-procedure. In patients who had renal denervation, left ventricular mass was reduced, whereas in the control group left ventricular mass continued to increase and diastolic function deteriorated during the follow-up period. Additionally, patients whose left ventricular mass decreased

also showed a significant increase in left ventricular ejection fraction and an improvement in diastolic function. Importantly, improvement in left ventricular mass and ejection fraction were greater in patients whose systolic blood pressure decreased the most.

The effect of renal denervation on atrial fibrillation (AF) was studied by Pokushalov *et al.*³⁶ Twenty-seven patients with AF and resistant hypertension were recruited into the study. Fourteen of these patients were treated with pulmonary vein isolation and 13 with pulmonary vein isolation in combination with renal denervation. At one-year follow-up, 69% of the subjects who underwent both pulmonary vein isolation and renal denervation were free of AF in addition to having a major reduction in blood. On the other hand, 71% of the subjects who underwent only pulmonary vein isolation had recurrent AF at the one-year time point. In addition, combined treatment with pulmonary vein isolation and renal denervation gave rise to a reduction in left ventricular mass.

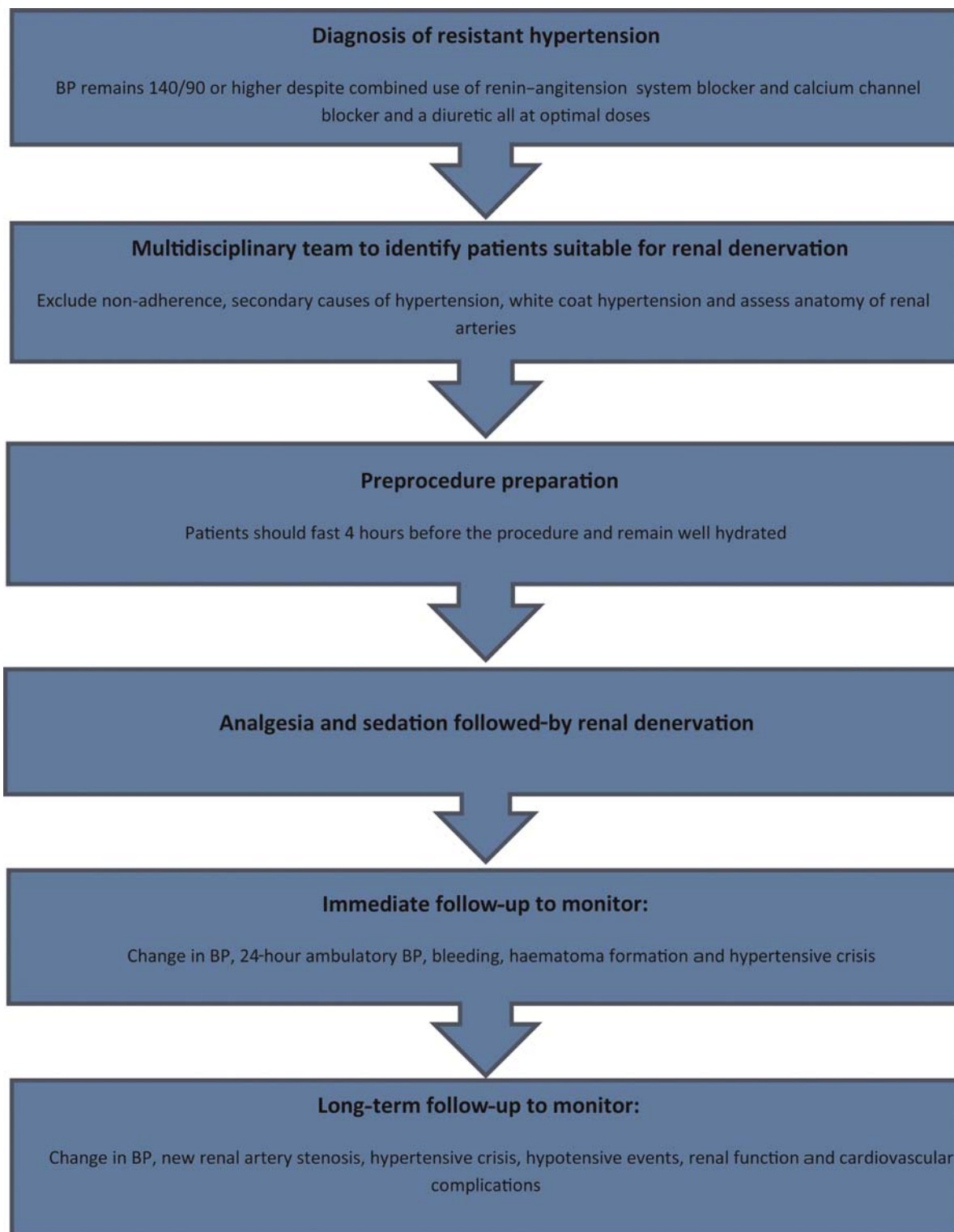
In another study, patients with resistant hypertension and sleep apnoea were treated with renal denervation; in addition to achieving a major reduction in blood pressure, improvements in patients' sleep apnoea and HbA1c level were noted, suggesting that renal denervation might help with glycaemic control in addition to hypertension control. However, the sample size was small in this study and further trials with larger numbers of patients are required to confirm these results.³⁷

Conclusion

Hypertension is a major health problem which affects large numbers of people worldwide and contributes to adverse cardiovascular outcomes. Although many patients with hypertension are successfully treated pharmacologically to control their blood pressure, a proportion of hypertension patients sustain elevated blood pressure despite being on at least three different classes of anti-hypertensive medication at optimal doses. Catheter-based renal denervation is a technique that shows much promise in treatment of such patients. Studies to date suggest that renal denervation therapy results in large falls in blood

Figure 1

Summary of place of renal denervation therapy in management of resistant hypertension, based on National Institute of Health and Clinical Excellence guidelines and Joint British Societies' consensus summary statement on renal denervation for resistant hypertension^{39,40}



pressure while at the same time being a relatively safe procedure. It may also give rise to regression of left ventricular hypertrophy and improvement of blood glucose levels and AF. In addition, a study by Geisler *et al.*³⁸ showed that catheter-based renal denervation is cost-effective technique for treatment of resistant hypertension.

The guidelines published by NICE in 2012³⁹ state that catheter-based renal denervation should be considered for patients with resistant hypertension who fail to respond to combination antihypertensive medication at maximum tolerated doses (Figure 1). A multidisciplinary team should decide which patients are suitable for the procedure, and the procedure should be carried out by a professional who is experienced in endovascular procedures and at a centre where emergency complications such as perforation of the renal artery and adverse events can be treated immediately and safely. The Joint British Societies' consensus summary statement on renal denervation for resistant hypertension supports the NICE guidelines and recommends that centres should have good capacity for interventional radiology and cardiology in addition to having CT and MRI imaging and catheter laboratory facilities available. Renal denervation centres are also expected to have a team of hypertension specialists and at least two professionals who can carry out the procedure.⁴⁰

However, it must be borne in mind that renal denervation therapy is relatively new and longer follow-up (including from registries) is needed to identify any potential long-term complications. For instance, one case report in the literature is of a patient who, following catheter-based renal denervation for treatment of resistant hypertension, developed >50% renal artery stenosis and recurrence of hypertension five months following the procedure.⁴¹ In addition, it is unclear whether the denervated sympathetic nerves can regrow and re-innervate the renal arteries, and this needs further investigation; patients need to be followed up in order to investigate this issue long-term as one study has shown that there is a risk of regrowth of sympathetic nerves within a few years following the denervation procedure.^{42, 43} A clinical trial called Symplicity HTN-3 is currently ongoing in the USA to study the effects of renal denervation in patients with resistant hypertension in more detail; it will be the largest

randomised trial to date of the procedure, aiming in a single-blind fashion to study 530 patients with systolic blood pressure of ≥ 160 mmHg despite being on 3 different types of antihypertensive medication at maximum tolerated doses. Subjects will be unblinded six months after the procedure, and those in the control group will at that point be offered renal denervation. All of the subjects participating in this trial will be followed up for three years.⁴⁴ The results from this trial should help clarify whether the procedure is indeed as effective and as safe as the data so far suggest.

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