Chapter 7
Renal Sympathetic Denervation

Markus P. Schlaich

Introduction

Hypertension affects an estimated 1 billion adults globally representing a major cardiovascular epidemic [1]. Despite the availability of safe and effective antihypertensive pharmacotherapies, hypertension management at the population level continues to remain suboptimal [2, 3] with predictions that approximately 50 % of adults in developed countries will meet the clinical criteria for hypertension by 2025 [4]. Several factors are known to interfere with adequate blood pressure (BP) control including excessive dietary sodium intake, use of medications that can raise BP, non-adherence with prescribed medication, physician inertia and others. The management of hypertension is further complicated by a subset of patients who, despite appropriate lifestyle modification and adherence to combination therapy, remain above target BP values, a phenomenon referred to as treatment resistant hypertension.

Resistant hypertension is commonly defined as office systolic BP ≥ 140 mmHg (≥ 130 mmHg for patients with type 2 diabetes) despite concurrent use of ≥ 3 antihypertensive agents of different classes (one being a diuretic) at maximal tolerated doses [5]. Optimising BP control in patients with resistant hypertension is of major clinical importance as these individuals are at significantly greater risk of target organ damage (including left ventricular hypertrophy (LVH), hypertensive retinopathy and renal disease) and major cardiovascular events compared with patients on combination therapy with controlled BP [6].

Latest findings from the USA indicate that ~ 13 % of adults that are being treated for elevated BP have resistant hypertension [7] with 1 in 50 patients newly diagnosed with hypertension developing resistant hypertension within a median of 1.5 years from initiating pharmacotherapy [6].

M. P. Schlaich (✉)
Neurovascular Hypertension and Kidney Disease Laboratory, Baker IDI Heart and Diabetes Institute, 75 Commercial Road, Melbourne, VIC 3004, Australia
e-mail: markus.schlaich@bakeridi.edu.au

M. R. Weir, E. V. Lerma (eds.), *Chronic Kidney Disease and Hypertension,*
Clinical Hypertension and Vascular Diseases, DOI 10.1007/978-1-4939-1982-6_7

Recommendations for the pharmacologic management of resistant hypertension at present remain largely empiric due to lack of robust data from clinical trials that directly compare the various treatment options available. Current international guidelines advocate the use of the mineralcorticoid receptor antagonist, spironolactone, as part of combination therapy [8, 9]. However, long-term safety data, particularly in patients with impaired renal function, are limited.

In recent years, the novel technique of catheter-based renal sympathetic nerve ablation has emerged as a potential novel therapeutic approach to lower BP, particularly in patients with resistant hypertension. Through targeting the sympathetic nervous system directly, this treatment approach may theoretically prove to be of potential use in a number of other clinical conditions characterized by increased sympathetic drive.

Pathophysiology

Renal sympathetic nerves have been identified as key contributors in the multifactorial etiology of hypertension and specifically resistant hypertension [10]. Indeed, several studies show a direct positive relationship between BP and renal, cardiac and peripheral sympathetic activity in hypertensive patients [11–13].

Postganglionic sympathetic nerve fibres form a dense, neuronal network within the adventitia of the renal artery [14]. Efferent motor fibres innervate all renal structures, including the renal vasculature, tubules and the juxtaglomerular apparatus [15], while afferent sensory nerves connect the kidney with autonomic centres in the central nervous system [16].

Central sympathetic outflow to the kidneys via efferent sympathetic fibres modulates BP by stimulating the release of renin, increasing sodium and water reabsorption, and inducing renal vasoconstriction with effects on renal blood flow and glomerular flow rate.

Activation of renal sensory afferent nerve fibres through renal ischemia, injury or elevated adenosine concentrations [17] alters the activity of central integrative neuronal circuits that are involved in neuronal control of cardiovascular regulation. The resulting increase in efferent sympathetic outflow from the central nervous system to the kidneys and to other highly innervated organs (such as the heart and vasculature) contributes to the development and/or maintenance of hypertension.

The Sympathetic Nervous System as a Therapeutic Target

Targeting the sympathetic nerves directly to achieve improved BP control is by no means a new concept. Prior to the availability of antihypertensive medications, non-selective surgical sympathectomy was used to treat patients with malignant

hypertension in the 1930 and 1940s [18]. Despite impressive reductions in BP and improved long-term cardiovascular outcomes, the highly invasive procedure was abandoned since it was associated with high peri-operative mortality rate and plagued by unwanted and often debilitating side effects such as orthostatic hypotension, syncope, and erectile, bowel and bladder dysfunction [19].

In contrast, the recently introduced transcatheter based approach for renal sympathetic nerve ablation is a rapid, minimally invasive, percutaneous procedure that uses radiofreqency (RF) energy to specifically and selectively target the renal efferent and afferent nerves located in the adventitia of the renal arteries. With a guide catheter positioned in the renal artery via femoral access, the RF ablation catheter is advanced into the renal artery and connected to a RF generator. A series of RF ablations is then being delivered along each renal artery from distally to proximally with longitudinal and rotational separation to achieve circumferential coverage of the renal artery, thereby targeting the renal nerves located in the adventitia of the vessel wall. The procedure is carried out bilaterally in one session.

Since publication of the first in-human study in 2009 [20], over 8000 renal denervation procedures have been performed in patients with resistant hypertension worldwide. Trans-luminal radiofrequency ablation is the most commonly used modality, however, alternative approaches such as ultrasound, cryoablation and perivascular injection of neurotoxins have been used or are currently being investigated. More recently, in addition to the use of single-electrode catheters delivering 4–8 discrete RF ablations along the renal artery lumen, multielectrode and balloon-catheter systems have been introduced and may offer potential advantages including reduction in RF energy delivery time, reduced contrast load, more reproducible ablation patterns and improved catheter positioning.

Indeed, preliminary findings for these second-generation systems are encouraging, with BP reductions comparable to the initial single-electrode systems [21, 22]. However, long-term safety and efficacy data from larger cohorts are required before these novel systems can be recommended for general use.

In the past year, The European Society of Cardiology (ECS) and The European Society of Hypertension (ESH) have released practical recommendations on the use of renal denervation in clinical practice [23, 24] (Fig. 7.1). The expert committees state that only patients with (severe) treatment-resistant hypertension, diagnosed by a hypertension specialist and confirmed with 24-h ambulatory blood pressure monitoring (ABPM), should be considered for the procedure. Secondary causes of resistant hypertension such as primary hyperaldosteronism, renal artery stenosis and obstructive sleep apnoea should also be ruled out or treated accordingly.

To maximise safety, the committees recommend that patients who have previously undergone renal artery intervention, have evidence of renal artery atherosclerosis or impaired kidney function (estimated glomerular filtration rate (eGFR) <45 ml/min per 1.73 m^2) be exempt. Anatomical contraindications including multiple renal arteries, one kidney or a main renal artery of <4 mm diameter or length <20 mm should also exclude a patient from undergoing the procedure.

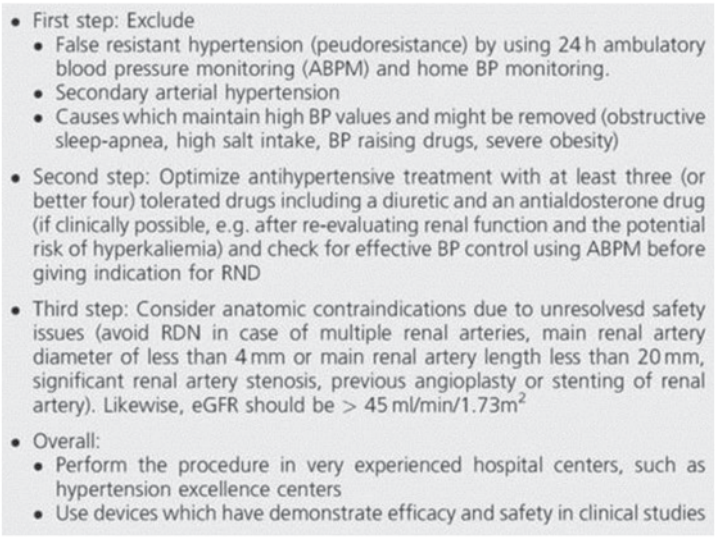

Fig. 7.1 Practical recommendations for the use of renal denervation in clinical practice according to the European Society of Hypertension. (Reprinted from Schmieder et al. [23]. With permission from Wolters Kluwer Health)

Clinical Trial Data on Catheter-Based Renal Sympathetic Denervation

The long-term safety and efficacy of catheter-based renal denervation to control BP has, to date, been evidenced by the Symplicity Clinical Trial Program. In 2009, the first proof-of-principle trial (Symplicity HTN-1) [20] was undertaken in 45 patients with resistant hypertension with an inclusion systolic BP threshold of > 160 mmHg (> 150 mmHg for patients with diabetes). Office BP was significantly reduced by −14/−10 mmHg (SBP/DBP) at 1 month after renal denervation with more pronounced reductions of −22/−11 mmHg and −27/−17 mmHg observed at 6 and 12 months, respectively. Renal sympathetic nerve activity as assessed by renal noradrenaline spillover was reduced on average by 47 %, confirming the impact of the denervation procedure on renal sympathetic nerve activity. Central sympathetic outflow, as assessed by microneurography, was also reduced in treated patients [25]. Importantly, no major procedure-related adverse events were reported.

As observed in a larger, extended Symplicity HTN-1 cohort ($n = 153$), the treatment effect on BP was sustained at 24 months [26] and, most recently, at 36 months [27], suggesting the absence of functionally relevant reinnervation of sympathetic nerves (Fig. 7.2). Four complications in the cohort included one renal artery dissection and three femoral artery pseudo-aneurysms. In 81 patients with magnetic resonance angiography, CT or duplex renal artery assessment post denervation, no stenosis was identified at sites where denervation was performed.

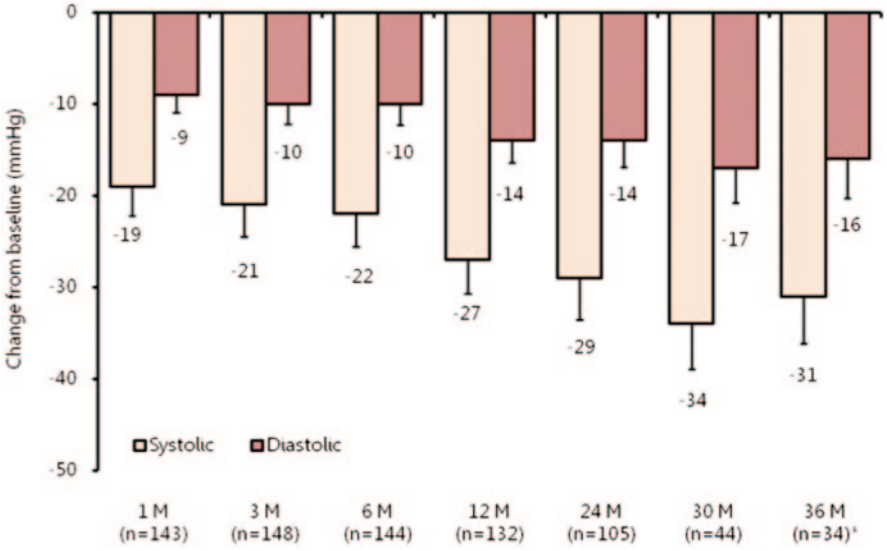

Fig. 7.2 Mean changes in office-based BP after renal denervation with up to 36-month follow-up in the extended Symplicity HTN-1 cohort ($n=153$). Error *bars* represent 95 % confidence intervals (CIs). Compared to baseline, significant differences in office-based BP were observed for patients at all reported time points during the 36-month follow-up period ($P<0.01$). *Asterisk* denotes number of patients with data available at time of data-lock

Encouraging results from the initial Symplicity HTN-1 trial led to the conduct of Symplicity HTN-2, a multicentre, prospective, randomized controlled trial involving 106 resistant hypertensive patients from 24 centres across Europe, Australia and New Zealand [28]. Of the 49 patients who immediately underwent renal denervation, mean office BP at 6 months significantly decreased by −32/−12 mmHg with no change in BP reported in the control group ($n=51$) assigned to standard pharmacological therapy (Fig. 7.3).

A subset of patients in the Symplicity HTN-2 trial (20 in the RDN group and 25 in the control group) underwent ABPM at 6 months, and the mean reduction in BP was 11/7 mmHg in patients with RDN, whereas there was no significant change in controls. Not surprisingly, the reduction in ABPM was less pronounced than the reduction in office BP. Other trials have confirmed that RDN causes greater reductions in office BP than ambulatory BP; however, the magnitude of the difference between office BP and ambulatory BP changes appears to be somewhat more pronounced than that observed in BP-lowering trials using pharmacological approaches.

Renal artery imaging at follow-up ($n=43$) confirmed the safety of the procedure with no reported incidence of renal artery stenosis or aneurismal deformation.

Recently, 12-month follow-up data from 47 patients in the Symplicity HTN-2 trial were published [29]; also included were 6-month post-denervation data for 35 control patients who, per-protocol, elected to undergo to the procedure after randomization. Compared to at baseline, there was no additional reduction in patient's office BP at 12 months compared to at 6 months ($P=0.16$; Fig. 7.3).

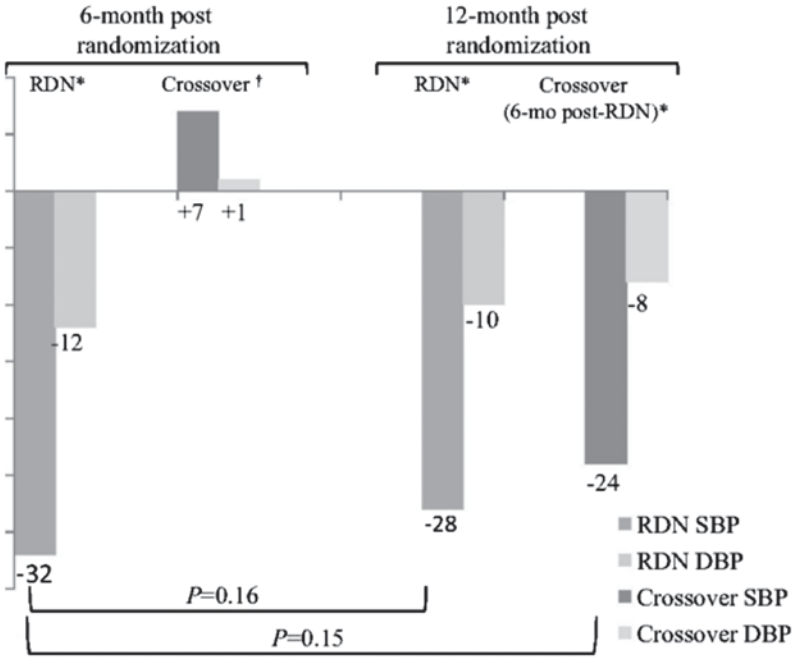

Fig. 7.3 Mean change in office-based BP after renal denervation at 6 and 12 months in the Simplicity HTN-2 trial. Both the initial renal denervation group and the crossover group denervated at 6 months after randomization experienced significant drops in systolic and diastolic BP. *RDN* denotes patient group immediately assigned to renal denervation at baseline, *crossover* denotes patient group who underwent renal denervation after randomization, *DBP* diastolic blood pressure, *SBP* systolic blood pressure. *Asterisks* denote $P<0.001$ for *SBP* and *DBP* change after renal denervation; the *dagger symbol* denotes $P=0.026$ for *SBP* change from baseline and $P=0.066$ for DBP change from baseline for the crossover group before denervation at 6 months (Reprinted from Esler et al. 2012. With permission from Wolters Kluwer Health)

The magnitude of SBP reduction at 12 months was, however, consistent with that observed in the first Symplicity HTN-1 trial (−28 vs. −27 mmHg). Mean change in office BP at 6 months was also shown to be comparable between patients assigned to immediate renal denervation and those who underwent the procedure after randomization ($P=0.15$).

In terms of safety, only two peri-procedural events were reported. One control patient experienced a femoral artery pseudoaneurysm prior to renal denervation that was resolved without further sequelae. A second control patient was hospitalised following renal denervation for a hypotensive episode that was managed with a reduction in their antihypertensive medication.

In both cohorts, renal denervation preserved kidney function as evidenced by nonsignificant changes in eGFR, serum creatinine and Cystatin C at 6 and 12 months. The observation supports a recent study of 88 patients with resistant hypertension who had a preserved eGFR 6 months post renal denervation [30].

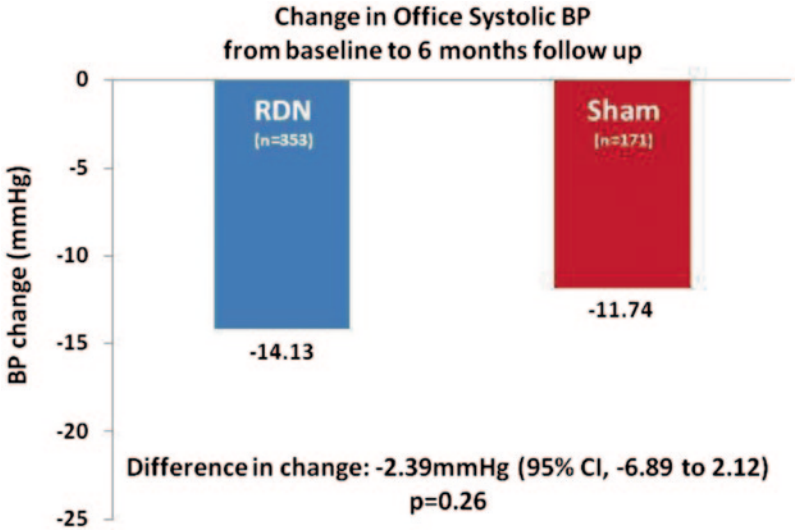

Fig. 7.4 Mean change in office systolic BP from baseline to 6-month follow-up in the Symplicity HTN-3 trial. A significant change from baseline to 6 months in office systolic blood pressure was observed in both study groups. The between-group difference (the primary efficacy end point) did not meet a test of superiority with a margin of 5 mmHg.

Symplicity HTN-3 [31] is the largest clinical trial on the safety and efficacy of renal denervation thus far, comprising a total of 535 patients with resistant hypertension randomized in a 2:1 ratio to receive renal denervation or a sham procedure. As the US pivotal trial seeking FDA approval, it was rigorously designed taking into account limitations that have been identified with Symplicity HTN-1 and 2. As such, patients had to have a systolic office BP of ≥160 mmHg while being on *full* doses of 3 or more antihypertensive drugs, including a diuretic. Ambulatory BP monitoring was mandatory and the 24-hour average BP had to be ≥135 mmHg to be included. Randomization occurred in the catheter lab after confirmation of suitable anatomy by renal angiogram. Patients were followed up by physicians blinded to the patient's randomization status. The primary safety end point was a composite of major adverse events at 1 month. The primary efficacy end point of the study was the difference in the reduction of systolic office BP between the renal denervation and the sham group with a 5-mmHg superiority margin.

The primary safety end point was met with no difference in the major adverse event rate between the two groups (1.4% in the renal denervation group vs. 0.6% in the sham-procedure group). However, while there was a significant reduction in systolic office BP of −14.1±23.9 mmHg ($P<0.001$) at 6-month follow-up in the renal denervation group, the difference in the change of BP with a superiority margin of 5% (−2.39 mmHg; 95% CI, −6.89–2.12; $P=0.26$) was not statistically significant from that seen in the sham-procedure group (−11.7±25.9 mmHg; $P<$ 0.001; Fig. 7.4), therefore the primary end point was not met. Similarly, the difference in the reduction of ABPM between the two groups, a secondary efficacy end

point was also not met (RDN, −6.75 ± 15.11 mmHg vs. Sham, −4.79 ± 17.25 mmHg; difference in changes, −1.96 (95 % CI, −4.97–1.06); $P = 0.98$).

The results from this trial were in stark contrast to the results of all other studies using different denervation systems, most of which were uncontrolled studies, and were considered by many as a substantial setback for renal denervation as a therapeutic approach to resistant hypertension. Indeed, the trial was excellently designed and the results highlighted the relevance of a sham control in device-based studies. However, several aspects relating primarily to the conduct of the study have been criticized and discussed as potential contributors to the failure of the trial to meet its efficacy end points. These include (i) inexperience of operators (88 centres participated in the trial with 111 operators performing RDN in 364 patients without previous experience in RDN); (ii) a substantial number of patients (~40 % in each group) had medication changes within the first 6 months after the RDN or sham procedure; (iii) no measures of drug adherence were obtained and (iv) no evidence of the degree of renal denervation achieved during the trial could be obtained. Furthermore, in contrast to previous studies, ~25 % of participants in Symplicity HTN-3 were of African American background with subgroup analysis indicating a potential difference in the BP response in this patient group. Future and more detailed analyses of Symplicity HTN-3 will have to determine whether or not these factors may have influenced the results of Symplicity HTN-3. Irrespective of these findings, more research in form of adequately designed studies will be required to ultimately determine the role of RDN in the treatment of resistant hypertension.

Possible Utility of Renal Sympathetic Ablation Beyond Resistant Hypertension

Preliminary studies suggest that catheter-based renal denervation may have therapeutic benefits, beyond BP control, in patients at high risk of cardiovascular events.

Excessive sympathetic activation is a hallmark of both chronic kidney disease (CKD) and end-stage renal disease (ESRD). In the vast majority of patients, chronic elevation in BP from sympathetic overdrive potentiates the progressive deterioration of renal function and leads to increased risk for serious cardiovascular events [32, 33]. Two pilot trials were recently undertaken to assess the feasibility and short-term safety of renal denervation in patients with CKD [34] and ESRD [35]. To date, only patients with normal kidney function (eGFR >45 mL/min per 1.73 m^2) have been assessed in large clinical cohorts [28, 29].

In 15 patients with resistant hypertension and stage 3–4 CKD (mean creatinine-based eGFR 31.2 [SD:8.9] mL/min per 1.73 m^2), renal denervation was shown to safely reduce seated office and night time BP (as measured by 24-h ABPM) by −32/−15 mmHg and −10/−3 mmHg, respectively, at 6 months. Importantly, angiographic evaluation after the procedure revealed no compromise of treated arteries or

disturbances in renal blood flow, electrolytes and eGFR. Improvements in peripheral arterial stiffness were also observed at 3 months.

For nine patients with ESRD and uncontrolled BP, a sustained reduction in office SBP of −18, −16 and −28 mmHg at 3, 6 and 12 months, respectively, was observed following renal denervation. Patients also demonstrated a reduction in both sympathetic outflow, as measured by muscle sympathetic nerve activity, and in renal and whole body noradrenaline release at 3 months ($n=2$). Anatomical limitations prevented three patients from undergoing renal denervation. Two patients also developed peri-operative femoral pseudo-aneurysms that resolved without further sequelae. Larger clinical trials are now warranted to substantiate these initial findings and determine whether renal denervation may represent a useful therapeutic approach in patients with impaired kidney function.

Chronic activation of the central sympathetic nervous system has also been implicated in the initiation and progression of several cardiovascular conditions that increase morbidity and mortality, including LVH, cardiac arrhythmias and chronic heart failure, at times in the absence of elevated BP [36]. Brandt et al. investigated the impact of renal denervation on LVH in 46 patients with resistant hypertension [37] and found the procedure significantly reduced LV mass, increased LV ejection fraction and improved diastolic function at 1 and 6 months.

A recent pilot study [38] evaluated the safety of renal denervation in seven normotensive patients with chronic systolic heart failure. At 6 months, all patients showed an improvement in their functional capacity (as assessed by a 6-min walk test) and overall quality of life. Of note, a recent study confirmed a beneficial effect on health-related quality of life after renal denervation [39]. Importantly, no procedural complications or symptomatic adverse effects were reported. Renal haemodynamics and function were also preserved.

Atrial fibrillation (AF) is associated with a sustained elevation in BP and represents the most common clinically significant cardiac arrhythmia. Usual treatment for AF includes catheter ablation to disconnect the pulmonary veins from the left atrium (known as pulmonary vein isolation; PVI). In patients with resistant hypertension, a combined therapy of PVI and renal denervation ($n=13$) significantly lowered office BP and had a salutary effect on AF patterns compared to PVI alone ($n=14$) [40]. At 12 months, 69 % of patients assigned to PVI with renal denervation were AF-free compared to 29 % assigned to PVI only. Patients on combined therapy also demonstrated a significant and sustained BP reduction of −25/−10 mmHg and reduction in LV mass of approximately 10 % at follow-up.

Renal denervation has recently been shown to improve central haemodynamics in patients with resistant hypertension [41]. In addition to lowering peripheral BP, the procedure significantly improved heart rate, central aortic BP and arterial stiffness (as measured by pulse wave velocity) in 110 patients at 1 month compared to controls ($n=10$) assigned to standard pharmacotherapy.

Current Limitations and Future Perspectives

Renal denervation has emerged as an appealing therapeutic approach for patients who are unable to achieve BP control with standard pharmacotherapy. However, the data from Symplicity HTN-3, which included a sham control, have casted doubt on the efficacy of RDN in this setting. Further well-designed clinical trials including a sham control will be required for regulatory purposes to ultimately proof or disproof its clinical utility. Furthermore, before this procedure can become part of routine clinical care several other areas require further investigation.

There is concern that sympathetic reinnervation may occur in patients who undergo the procedure, as seen in animal studies [42] and after heart transplantation [43]. At present, long-term follow-up data are limited with only one study demonstrating a sustained BP reduction at 36 months [27]. Additional studies are urgently needed to confirm the long-term efficacy of the procedure.

It is apparent that renal denervation does not cause universal BP reduction, and identifying predictors for non-response may help identify patients that will benefit specifically from the procedure.

A recent study compared the cost-effectiveness of renal denervation compared to more established medical treatments to lower BP [44], with impressive reductions in cardiovascular events (21–32%) over 10 years predicted. The long-term impact of renal denervation on CV morbidity and mortality is yet to be elucidated and will not be known for some time.

There is substantial interest in renal denervation as a treatment for less severe forms of hypertension. Initial data from two studies are conflicting, with one small case series of 12 patients not showing a significant BP reduction after renal denervation, [45] while a slightly larger study ($n=20$) demonstrated a BP reduction of −13.1/−5.0 mmHg at 6 months [46]. Most recently, a report on a cohort of 54 patients with moderate resistant hypertension defined as office BP ≥140/90 mmHg and <160/100 mmHg on an average of 5.1 antihypertensive drugs and 24-h ambulatory BP ≥130/80 mmHg demonstrated a reduction of office BP by 13/7 mmHg 6 months after RDN [47]. Office BP was controlled below 140/90 mmHg in 51% of the patients and 37% of patients reduced their antihypertensive medications. In the patients ($n=36$) who had ABPM before and 6 months after the procedure, there was a reduction in average ambulatory BP of 14/7 mmHg.

Clearly, randomized sham-controlled clinical trials in these cohorts will be required to properly define the usefulness of renal sympathetic denervation.

Conclusions

Resistant hypertension is a clinically important condition that is associated with significant cardiovascular risk. The majority of data from the Symplicity Clinical Trials Program and early-phase studies using various RDN modalities in high-risk patient cohorts suggest a therapeutic benefit of this approach in regards to BP reduction;

however, the most rigorous trial conducted thus far clearly failed to demonstrate a BP reduction beyond that of a sham procedure. Whether the criticisms raised in regards to the conduct of the study are valid or not will have to be determined.

The potential clinical utility of RDN may extend to other conditions characterized by chronic sympathetic overactivity, as indicated by several small but mainly uncontrolled studies. At this stage, RDN should be performed primarily within randomized controlled clinical trials to identify those patient cohorts that may derive benefit from RDN.

Acknowledgments The manuscript is supported by a Senior Research Fellowship from the National Health and Medical Research Council (NHMRC) of Australia.

References

1. World Health Organisation. Global status report on noncommunicable diseases 2010: WHO 2011.
2. Wolf-Maier K, Cooper RS, Kramer H, Banegas JR, Giampaoli S, Joffres MR, et al. Hypertension treatment and control in five European countries, Canada, and the United States. Hypertension. 2004;43(1):10–7.
3. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, et al. Heart disease and stroke statistics-2011 update: a report from the American Heart Association. Circulation. 2011;123(4):e18–209.
4. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet. 2005;365(9455):217–23.
5. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Circulation. 2008;117(25):e510–26.
6. Daugherty SL, Powers JD, Magid DJ, Tavel HM, Masoudi FA, Margolis KL, et al. Incidence and prognosis of resistant hypertension in hypertensive patients. Circulation. 2012;125(13):1635–42.
7. Persell SD. Prevalence of resistant hypertension in the United States, 2003–2008. Hypertension. 2011;57(6):1076–80.
8. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, et al. Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Hypertension. 2008;51(6):1403–19.
9. Krause T, Lovibond K, Caulfield M, McCormack T, Williams B. Management of hypertension: summary of NICE guidance. BMJ. 2011;343:d4891.
10. Esler M The sympathetic system and hypertension. Am J Hypertens. 2000;13(6 Pt 2): 99S−105.
11. Smith PA, Graham LN, Mackintosh AF, Stoker JB, Mary DA. Relationship between central sympathetic activity and stages of human hypertension. Am J Hypertens. 2004;17(3):217–22.
12. Esler M, Lambert G, Jennings G. Regional norepinephrine turnover in human hypertension. Clin Exp Hypertens A. 1989;11(Suppl 1):75–89.
13. Schlaich MP, Lambert E, Kaye DM, Krozowski Z, Campbell DJ, Lambert G, et al. Sympathetic augmentation in hypertension: role of nerve firing, norepinephrine reuptake, and Angiotensin neuromodulation. Hypertension. 2004;43(2):169–75.
14. DiBona GF. Physiology in perspective: the wisdom of the body. Neural control of the kidney. Am J Physiol Regul Integr Comp Physiol. 2005;289(3):R633–41.

15. Barajas L. Innervation of the renal cortex. Fed Proc. 1978;37(5):1192–201.
16. Kopp UC. Renorenal reflexes: interaction between efferent and afferent renal nerve activity. Can J Physiol Pharmacol. 1992;70(5):750–8.
17. Esler M. The 2009 Carl Ludwig Lecture: pathophysiology of the human sympathetic nervous system in cardiovascular diseases: the transition from mechanisms to medical management. J Appl Physiol. 2010;108(2):227–37.
18. Morrissey DM, Brookes VS, Cooke WT. Sympathectomy in the treatment of hypertension; review of 122 cases. Lancet. 1953;1(6757):403–8.
19. Allen TR. Current status of lumbar sympathectomy. Am Surg. 1976;42(2):89–91.
20. Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet. 2009;373(9671):1275–81.
21. Ormiston JA, Watson T, van Pelt N, Stewart R, Haworth P, Stewart JT, et al. First-in-human use of the OneShot renal denervation system from Covidien. EuroIntervention. 2013;8(9):1090–4.
22. Mabin T, Sapoval M, Cabane V, Stemmett J, Iyer M. First experience with endovascular ultrasound renal denervation for the treatment of resistant hypertension. EuroIntervention. 2012;8(1):57–61.
23. Schmieder RE, Redon J, Grassi G, Kjeldsen SE, Mancia G, Narkiewicz K, et al. ESH position paper: renal denervation—an interventional therapy of resistant hypertension. J Hypertens. 2012;30(5):837–41.
24. Mahfoud F, Luscher TF, Andersson B, Baumgartner I, Cifkova R, Dimario C, et al. Expert consensus document from the European Society of Cardiology on catheter-based renal denervation. Eur Heart J. 2013;34:2149–57
25. Hering D, Lambert EA, Marusic P, Walton AS, Krum H, Lambert GW, et al. Substantial reduction in single sympathetic nerve firing after renal denervation in patients with resistant hypertension. Hypertension. 2013;61(2):457–64.
26. Symplicity HTN-1 Investigators. Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. Hypertension. 2011;57(5):911–7.
27. Krum H, Schlaich M, Sobotka PA, Esler M, Mahfoud F, Bohm M, et al. TCT-12 long-term follow-up of catheter-based renal denervation for resistant hypertension confirms durable blood pressure reduction. JACC. 2012;60(17):Suppl B3.
28. Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Bohm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. Lancet. 2010;376(9756):1903–9.
29. Esler MD, Krum H, Schlaich M, Schmieder RE, Bohm M, Sobotka PA. Renal sympathetic denervation for treatment of drug-resistant hypertension: one-year results from the Symplicity HTN-2 randomized, controlled trial. Circulation. 2012;126(25):2976–82.
30. Mahfoud F, Cremers B, Janker J, Link B, Vonend O, Ukena C, et al. Renal hemodynamics and renal function after catheter-based renal sympathetic denervation in patients with resistant hypertension. Hypertension. 2012;60(2):419–24.
31. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, et al. A controlled trial of renal denervation for resistant hypertension. N Engl J Med. 2014;370(15):1393–401.
32. Schlaich MP, Sobotka PA, Krum H, Whitbourn R, Walton A, Esler MD. Renal denervation as a therapeutic approach for hypertension: novel implications for an old concept. Hypertension. 2009;54(6):1195–201.
33. Schlaich MP, Socratous F, Hennebry S, Eikelis N, Lambert EA, Straznicky N, et al. Sympathetic activation in chronic renal failure. J Am Soc Nephrol. 2009;20(5):933–9.
34. Hering D, Mahfoud F, Walton AS, Krum H, Lambert GW, Lambert EA, et al. Renal denervation in moderate to severe CKD. J Am Soc Nephrol. 2012;23(7):1250–7.
35. Schlaich MP, Bart B, Hering D, Walton A, Marusic P, Mahfoud F, et al. Feasibility of catheter-based renal nerve ablation and effects on sympathetic nerve activity and blood pressure in patients with end-stage renal disease. Int J Cardiol. 2013;168:2214–20.

36. Malpas SC. Sympathetic nervous system overactivity and its role in the development of cardiovascular disease. Physiol Rev. 2010;90(2):513–57.
37. Brandt MC, Mahfoud F, Reda S, Schirmer SH, Erdmann E, Bohm M, et al. Renal sympathetic denervation reduces left ventricular hypertrophy and improves cardiac function in patients with resistant hypertension. J Am Coll Cardiol. 2012;59(10):901–9.
38. Davies JE, Manisty CH, Petraco R, Barron AJ, Unsworth B, Mayet J, et al. First-in-man safety evaluation of renal denervation for chronic systolic heart failure: primary outcome from REACH-Pilot study. Int J Cardiol. 2013;162(3):189–92.
39. Lambert GW, Hering D, Esler MD, Marusic P, Lambert EA, Tanamas SK, et al. Response to quality of life after renal denervation. Hypertension. 2013;61(4):e39.
40. Pokushalov E, Romanov A, Corbucci G, Artyomenko S, Baranova V, Turov A, et al. A randomized comparison of pulmonary vein isolation with versus without concomitant renal artery denervation in patients with refractory symptomatic atrial fibrillation and resistant hypertension. J Am Coll Cardiol. 2012;60(13):1163–70.
41. Brandt MC, Reda S, Mahfoud F, Lenski M, Bohm M, Hoppe UC. Effects of renal sympathetic denervation on arterial stiffness and central hemodynamics in patients with resistant hypertension. J Am Coll Cardiol. 2012;60(19):1956–65.
42. Carlstedt T, Dalsgaard CJ, Molander C. Regrowth of lesioned dorsal root nerve fibers into the spinal cord of neonatal rats. Neurosci Lett. 1987;74(1):14–8.
43. Bengel FM, Ueberfuhr P, Schiepel N, Nekolla SG, Reichart B, Schwaiger M. Effect of sympathetic reinnervation on cardiac performance after heart transplantation. N Engl J Med. 2001;345(10):731–8.
44. Geisler BP, Egan BM, Cohen JT, Garner AM, Akehurst RL, Esler MD, et al. Cost-effectiveness and clinical effectiveness of catheter-based renal denervation for resistant hypertension. J Am Coll Cardiol. 2012;60(14):1271–7.
45. Brinkmann J, Heusser K, Schmidt BM, Menne J, Klein G, Bauersachs J, et al. Catheter-based renal nerve ablation and centrally generated sympathetic activity in difficult-to-control hypertensive patients: prospective case series. Hypertension. 2012;60(6):1485–90.
46. Kaltenbach B, Franke J, Bertog SC, Steinberg DH, Hofmann I, Sievert H. Renal sympathetic denervation as second-line therapy in mild resistant hypertension: a pilot study. Catheter Cardiovasc Interv. 2013;81(2):335–9.
47. Ott C, Mahfoud F, Schmid A, Ditting T, Sobotka PA, Veelken R, et al. Renal denervation in moderate treatment-resistant hypertension. J Am Coll Cardiol. 2013;62(20):1880–6.