Catheter-based Renal Sympathetic Denervation – Long-term Symplicity™ Renal Denervation Clinical Evidence, New Data and Future Perspectives

Katrina Mountfort, Medical Writer, Radcliffe Cardiology

Based on Presentations at a Medtronic Sponsored Symposium held at EuroPCR 2013, Paris, France, on 21 May 2013

The article was reviewed for accuracy by the presenters:
Felix Mahfoud,[1] Roland Schmieder,[2] Justin Davies,[3] David E Kandzari,[4] Joachim Weil[5] and Robert Whitbourn[6]

1. Klinik für Innere Medizin III, Kardiologie, Angiologie und Internistische Intensivmedizin, Universitätsklinikum des Saarlandes, Homburg/Saar, Germany; 2. Medizinische Klinik IV, Universitätsklinikum Erlangen, Erlangen, Germany; 3. Consultant Cardiologist, Hammersmith Hospital, Imperial College London, London, UK; 4. Chief Scientific Officer, Director, Interventional Cardiology, Piedmont Heart Institute, Atlanta, Georgia, US; 5. CardioMed Herzzentrum Nord, Sana Klinikum Lübeck, Akademisches Lehrkrankenhaus der Universität zu Lübeck, Lübeck, Germany; 6. Director, Cardiac Catheterization Labs and Coronary Intervention, The Cardiovascular Research Centre, University of Melbourne and Australian Catholic University, Melbourne, Australia

Abstract

Hypertension is one of the most prevalent chronic diseases worldwide and the incidence of resistant hypertension is increasing. Catheter-based renal denervation (RDN) offers a new approach to reaching blood pressure goals by targeting the renal nerves. The technique has demonstrated significant and sustained reductions in blood pressure (BP) in the Symplicity HTN-1 and Symplicity HTN-2 clinical trials. The Global SYMPLICITY Registry aims to demonstrate safety and effectiveness in a 'real-world' patient population. Real-world RDN experience has emphasised that patient selection is crucial to successful outcomes; a multidisciplinary referral network is recommended to increase awareness of the procedure and identify patients who are likely to respond best to RDN. Further advances in catheter technology have led to the development of the multi-electrode Symplicity Spyral™ multi-electrode catheter; preliminary data from the feasibility study using the Symplicity Spyral catheter indicate clinical efficacy and procedural safety with reduced procedure times. The Symplicity Spyral catheter is not yet commercially available. The indications of RDN may also expand beyond resistant hypertension – encouraging data have been seen in patients with moderate treatment resistant hypertension. Furthermore, RDN may be beneficial in other clinical states characterised by sympathetic nervous system overactivation including heart failure and chronic kidney disease. Additional data are needed to evaluate the efficacy of RDN in these disease states.

Keywords

Blood pressure, radiofrequency ablation, renal denervation, resistant hypertension, Symplicity

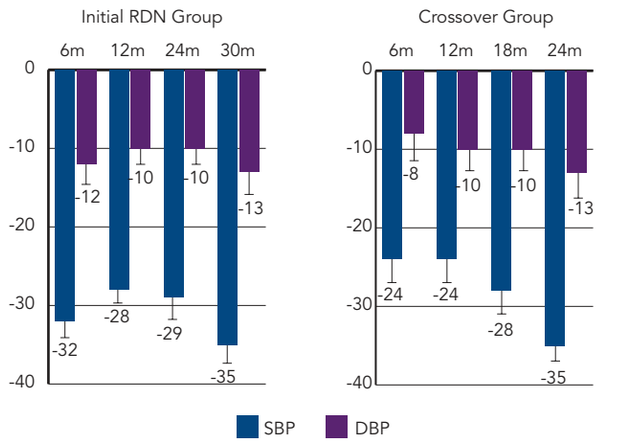
Disclosure: All authors have served either in a consultancy or advisory capacity, or on a speakers' bureau for Medtronic.
Acknowledgements: The speaking panel acknowledge Radcliffe Cardiology for providing writing and editing support.
Received: 20 July 2013 **Accepted:** 5 September 2013 **Citation:** *Interventional Cardiology Review*, 2013;8(2):118–23

Support: The publication of this article was supported by Medtronic. The views and opinions expressed are those of the speakers and not necessarily those of Medtronic.

Hypertension is one of the most important public health problems of the 21st century, with a global prevalence of around 30 %.[1] In 2010, it accounted for 7.5 million deaths worldwide, representing 12.8 % of the global total.[2] Furthermore, its prevalence is projected to rise to 1.5 billion hypertensive patients in 2025.[3] Despite the availability of numerous safe and effective antihypertensive medications, the proportion of hypertensive patients achieving recommended blood pressure (BP) targets is only around 50 %.[4] Resistant hypertension is generally defined as BP that remains high (>140/90 millimetres of mercury [mmHg]) despite the concomitant use of antihypertensive drugs from more than three drug classes, including a diuretic.[5] Estimates of its prevalence vary widely, but data from observational studies and clinical trials suggest that 8–30 % of treated hypertension patients have resistant hypertension.[6] Given that cardiovascular mortality doubles with each 20/10 mmHg increase in BP,[7] resistant hypertension represents a serious global health challenge.

New approaches to the treatment of patients with resistant hypertension are an important clinical need. Percutaneous catheter-based transluminal renal ablation (renal denervation [RDN]) is emerging as a novel treatment approach for resistant hypertension. Renal nerve activation contributes to the pathogenesis of hypertension as a result of renal vasoconstriction; renal blood flow and glomerular filtration rate (GFR) decrease; increased sodium reabsorption and renin release.[8,9] RDN, involving a multiple application of radiofrequency (RF) energy using a catheter, has been shown to provide an effective and

Figure 1: Symplicity HTN-2, Changes in Office Blood Pressure Over 30 Months



DBP = diastolic blood pressure; m = months; SBP = systolic blood pressure. Esler, 2013.[20] Reproduced from slide 14, Kandzari presentation.

Table 1: Overview of the Symplicity™ Renal Denervation Clinical Trial Programme

Trial	Description	n	Status
Symplicity HTN-1	Series of non-randomised pilot studies	153	Completed, 3 year follow-up data available
Symplicity HTN-2	1:1 randomisation	106	Completed enrolment, 2 year follow-up data available
SYMPLICITY HTN-3	Randomised controlled trial (2:1)	530	Enrolment completed May 2013
SYMPLICITY-HF	Feasibility study	40	Enrolling
Global SYMPLICITY Registry	Prospective, non-interventional registry	5,000	Enrolling
SYMPLICITY HTN-Japan	Randomised controlled trial (1:1)	100	Enrolling
SYMPLICITY HTN-4	Randomised controlled trial (2:1)	530–580	To start in latter half of 2013
SYMPLICITY HTN-India	Single-arm trial	40	Planned

safe means of reducing sympathetic outflow to and from the kidneys without adversely affecting other functions of the kidney.[10] It is a minimally invasive procedure, characterised by short recovery times and the absence of significant systemic side effects.[11] The treatment has resulted in significant and sustained BP reductions over 36 months in the majority of patients with resistant hypertension[12–14] and has been associated with improvements in health-related quality of life.[15] A recent study also suggested that RDN is a cost-effective strategy for resistant hypertension.[16]

Several devices have been approved for RDN, the most established of which is the Symplicity™ renal denervation system (Medtronic, Inc). The Symplicity Flex™ catheter is specifically designed for the renal anatomy, being non-occlusive and 6 French guiding catheter compatible. The Symplicity G2™ generator utilises specific algorithms that ensure optimal delivery of RF energy to the renal artery. The procedure requires application of RF energy to 4–6 locations within each of the renal arteries to effect renal nerve interruption. The technique is straightforward to perform – treatment of renal arteries without angiographic stenosis with the Symplicity Flex catheter requires two minutes duration per treatment for a total bilateral denervation time of 8–12 minutes. Its use is supported by extensive worldwide experience, including a clinical evaluation programme. This review will present the clinical evidence in support of RDN, as well as considering future perspectives on the technique.

The Symplicity™ Renal Denervation Clinical Trial Programme

Early clinical trial data showed that the use of the Symplicity RDN system was associated not only with reductions in systolic BP (SBP) and diastolic BP (DBP) but also with markers of hypersympathetic activity, such as reductions in muscle sympathetic activity and reductions in cardiac baroreflex sensitivity,[11] as well as a reduction in renal noradrenaline spillover.[17]

The first human clinical trial, Renal Denervation in Patients With Uncontrolled Hypertension (Symplicity HTN-1) (n=153), was an aggregate of multiple studies of patients with resistant hypertension (office SBP ≥160 mmHg with at least three or more antihypertensive medications, including a diuretic) and normal renal function (GFR >45 millilitres per minute [ml/min]).[12,17] At six months, 92 % of patients had an office BP reduction of ≥10 mmHg, with reductions in SBP and DBP of 25/11 mmHg, respectively (p<0.0001). Safety data were excellent – 97 % of patients had no complications. The four acute procedural complications included three pseudoaneurysms of the common femoral artery and one renal artery dissection, all managed without further sequelae. Three-year follow-up data showed no treatment-related vascular complications; no hypotensive events that required hospitalisation; no orthostatic hypotension; no electrolyte disturbances; and no significant changes in mean electrolytes or estimated GFR (eGFR).[18] Of the short-term follow-up renal imaging performed, no evidence of renal artery stenosis or abnormalities was noted in treated arteries.

The successful results of the Symplicity HTN-1 trial were expanded by the multicentre, prospective, randomised Renal Denervation in Patients With Uncontrolled Hypertension (Symplicity HTN-2) trial (n=106), in which patients with resistant hypertension and office SBP ≥160 mmHg (≥150 mmHg for patients with type 2 diabetes) were randomised to RDN immediately or after six months, without any change in the previous antihypertensive medication regimen. At six months, RDN was associated with BP reductions of 32/12 mmHg (p<0.0001),[13] showing superiority over medication management alone, and similar results were reported at two years.[19] Recently presented 30-month follow-up data showed durable BP reductions of 35/13 mmHg (p<0.01) in subjects available at data lock. At six months after randomisation, 46 of the 51 patients available for follow-up crossed over to RDN, 35 of which still met initial eligibility criteria. In the crossover group, a significant reduction in both SBP and DBP was of almost equal magnitude to that of the initial treatment cohort (see *Figure 1*).[20]

The Renal Denervation in Patients With Uncontrolled Hypertension (SYMPLICITY HTN-3) trial (n=530) is a multicentre, prospective randomised controlled study, which is blinded and includes a mask blinded (sham) procedure in the study design.[21] It will address ambulatory blood pressure monitoring (ABPM) as both an entry criteria and a powered secondary endpoint. In addition, a feasibility

study in heart failure (Renal Denervation in Patients With Chronic Heart Failure & Renal Impairment Clinical Trial [SYMPLICITY-HF], n=40), and a hypertension clinical trial in Japan (Renal Denervation by MDT-2211 System in Patients With Uncontrolled Hypertension [HTN-J], n=100) are underway. Further trials in India (Single-arm Study of Symplicity™ Renal Denervation System in Patients With Uncontrolled Hypertension in India) and the US (Renal Denervation in Patients With Uncontrolled Hypertension [SYMPLICITY HTN-4]) are planned (see *Table 1*). All of these trials, together with the Global Prospective Registry for Sympathetic Renal Denervation in Selected Indications Through 3-5 Years Registry (Global SYMPLICITY Registry) discussed below, will include over 320 sites and nearly 6,000 patients.

In summary, clinical trials to date investigating the safety and efficacy of RDN with the Symplicity RDN system for patients with resistant hypertension have demonstrated significant and durable reductions in BP; procedural, intermediate and long-term safety as well as preservation of electrolyte and human homeostasis. Ongoing evaluation should confirm the effectiveness of RDN in selected and broader patient populations.

The Global SYMPLICITY Registry

In addition to the Symplicity clinical trials, the Global SYMPLICITY Registry, which will include ≥5,000 patients in more than 200 sites worldwide, is being conducted.[22,23] Inclusion criteria are patients 18 years and older that are eligible for RDN and sign a patient consent form. The registry will also include patients with conditions characterised by an increase in sympathetic activity, including heart failure, chronic kidney disease, sleep apnoea and atrial fibrillation. The aims of this registry are to document the long-term safety and effectiveness of RDN; in everyday clinical practice; to monitor BP response in different nationalities and races; to identify patients who are likely to respond best to RDN and to monitor pleiotropic treatment effects, such as changes in glucose metabolism, renal and cardiac function. Secondary objectives include duration of BP lowering after treatment.[23]

The Global SYMPLICITY Registry is intended as an umbrella under which national registries, including the German Renal Denervation (GREAT) registry in Germany (n=1,000), the Korea Registry (n=102) and the South Africa Registry (n=400), will contribute data. The recommended follow-up schedule is three months, six months, one year, and each year up to five years after treatment.[23] Baseline and follow-up assessments will include patient demographics; physical measurements; office and 24-hour ambulatory BP, medication logs; quality of life; and heart rate. Vascular safety in the renal artery will be assessed and right ventricular imaging will also be conducted for those patients who receive cardiac imaging as per their standard of care, since it has been shown that RDN reduces heart rate.[24]

Patient selection is crucial to the success of RDN therefore subgroup analysis from the registry will be performed to determine whether any patient group especially benefits from the procedure. This will include renal function (eGFR <60 versus >60 ml/min/1.73 square metres [m^2]). The registry will also compare dippers (patients with lower BP at night) to non-dippers (characterised by an increased sympathetic activity and an indication of higher cardiovascular risk). Analyses will also focus on subgroups with left ventricular hypertrophy (LVH), an indicator of end-organ damage in arterial hypertension. The presence of LVH is associated with an increased rate of cardiovascular events and death independent of BP.[25] Subgroup analysis will also include patients with type 2 diabetes, impaired glucose tolerance, hyperinsulinemia, concomitant use of oral sympatholytic drugs, and consider age, heart rate and BP above and below median.

Changes in medication will also be recorded. It is recommended that baseline medication is maintained in order to accurately assess the net effect of RDN on BP, although in practice patients tend to manage their medications themselves. Poor compliance to therapy is a well-known problem in resistant hypertension; a recent study involving toxicological urine analysis found that drug adherence in resistant hypertension was only 47 %.[26] This leads to difficulties in terms of interpreting BP measurements and in obtaining an accurate diagnosis of resistant hypertension.

Safety endpoints will include vascular complications; renal artery perforation or dissections; renal artery re-interventions; new renal artery stenosis; hypertensive crisis; contrast nephropathy (acute eGFR drop of >25 % or new renal failure); new need for dialysis; and significant embolic event resulting in end-organ damage. Stroke, acute MI, end-stage renal disease, atrial fibrillation and mortality will also be investigated.

As of January 2013, data were available for 617 patients, the majority (60 %) of which had been treated according to the European Society of Cardiology (ESC) consensus guideline paper on RDN.[27] Preliminary six-month data demonstrated an excellent procedural and clinical safety profile, including significant reductions in both office and ambulatory BP compared to baseline.[23] In summary, the enrolment and analyses of the Global SYMPLICITY Registry continue to meet the goals of establishing the procedural safety and efficacy of RDN.

The Symplicity Spyral™ Multi-electrode Renal Denervation Catheter

Renal denervation using the Symplicity Flex catheter has demonstrated efficacy and safety both in clinical trial and real-world settings; however, it would be desirable to minimise the amount of treatment time required during the procedure. The Symplicity Spyral multi-electrode renal denervation catheter was designed with the goal of reducing procedure time while maintaining similar clinical outcomes and reassurance of success as compared to the original proven Symplicity Flex catheter. The Symplicity Spyral catheter has a helical-shape, and the electrode array consists of four independently selectable RF electrodes radially spaced by approximately 90 degrees to each other. The electrodes deliver energy simultaneously, decreasing the time for the ablation cycle to one minute per artery (see *Figure 2*) and the commercial catheter can be used for arteries with diameters between 3 and 8 millimetres (mm) ('one-size-fits-all').

Preclinical data using a porcine model showed that the ablation pattern achieved using the Symplicity multi-electrode catheter was consistent with the ablation pattern obtained with the Symplicity single-electrode catheter. At 28 days post-intervention, no difference in norepinephrine levels, a measure of renal sympathetic activity, was seen between the multi-electrode and single-electrode catheter; in both cases there was a significant reduction compared with the control kidneys. Histological evaluation also revealed no sign of injury to the renal artery.[28]

A feasibility study is underway to assess the efficacy of the Symplicity Spyral catheter in the acute setting. The feasibility study is expected to include up to 50 patients in total. The inclusion criteria are similar to those used in the Symplicity clinical trials. Initial results in 29 patients were presented at the 2013 EuroPCR meeting in Paris, France. The

mean BP at baseline was 182/94 mmHg, and participants were taking 4.7 medications. The mean procedure time for the Symplicity Spyral catheter (calculated as guide catheter removal – catheter insertion) was 21.2 minutes. Nearly all of the patients had an RF treatment time of one minute per artery; two patients received more than one treatment in a single artery. At one month, patients experienced an average office BP reduction of 16/7 mmHg from baseline ($p<0.001$), which was consistent to that achieved in the Symplicity-HTN trials. A reduction in heart rate of 4.3 beats per minute ($p<0.047$) and a decrease in pulse pressure of 8.8 mmHg ($p=0.004$) were also seen. The procedure had 96.6 % procedure success (defined as successful delivery of any RF in the absence of an in-hospital major adverse effect). One femoral pseudoaneurysm occurred in hospital at the access site requiring surgical intervention and one occurred at day three post-treatment requiring compression.[28]

In summary, in data generated to date, the Symplicity Spyral catheter had a safety profile consistent with the safety results demonstrated by the Symplicity Flex catheter; had demonstrated preclinical and clinical efficacy data consistent with the Symplicity Flex catheter; and confers the advantage of shorter treatment duration.

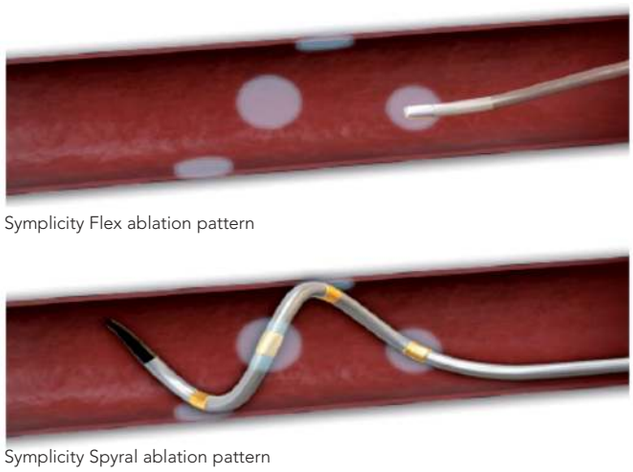
Effectiveness of Renal Denervation in Mild to Moderate Resistant Hypertension

The safety and efficacy of RDN for BP reduction in patients with severe resistant hypertension has been established. However, such patients represent only a small portion of the hypertensive community. Current studies are investigating the possibility of expanding the therapeutic indications for RDN, including the larger 'mild to moderate' resistant hypertension population. An ongoing observational non-randomised trial[29] (n=54) included patients with office BP above 140/90 mmHg and below 160/100 mmHg; all had been on three medications, one of which was a diuretic. The objectives were to analyse the reduction in office BP, as well 24-hour ABPM.

Preliminary data from this study show that the absolute reduction in office BP was 12.5/7.5 mmHg (17.6/8.8 mmHg in patients with available ABPM, n=36) after six months, numerically less than the reductions observed in the Symplicity HTN-1 and Symplicity HTN-2 clinical trials (see *Figure 3*).[29] This is unsurprising given the lower baseline BP in the patient population. Heart rate dropped significantly from 67 to 63 beats per minute. In 37 % of the patients, antihypertensive medication was reduced during the follow-up period, despite the guidance of the study protocol not to do so. Antihypertensive medication was not increased in any patient. In 51 % of the patients, office BP was controlled (defined as <140/90 mmHg) after RDN. Furthermore, there was a substantial reduction in 24-hour ambulatory BP (14.1/6.6 mmHg) (see *Figure 3*). An increasing body of evidence suggests that reduction of 24-hour ambulatory BP may provide superior cardiovascular risk reduction to office BP.[30] However, management decisions based on the interpretation of ABPM patterns are more complex than with office BP, and suitable educational processes are required.

In summary, although this was a small study and lacked a control group, the data indicated that RDN resulted in a substantial reduction in both office and 24-hour ambulatory BP in mild to moderate resistant hypertension. These results will need to be confirmed in a larger study. The SYMPLICITY HTN-4 trial, which is planned to commence enrolment in the latter half of 2013, will address this patient cohort, as well as the broader patient population.

Figure 2: Ablation Pattern in Symplicity Flex™ and Symplicity Spyral™ Catheters

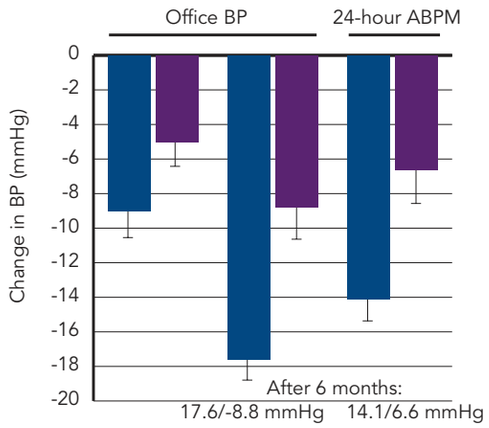


Symplicity Flex ablation pattern

Symplicity Spyral ablation pattern

Whitbourn, 2013,[28] reproduced from the EuroPCR presentation, slide 3.

Figure 3: Absolute Change in Office Blood Pressure and 24-hour Ambulatory Blood Pressure in Patients (n=36) with Available Ambulatory Blood Pressure Monitoring Before and After Renal Denervation



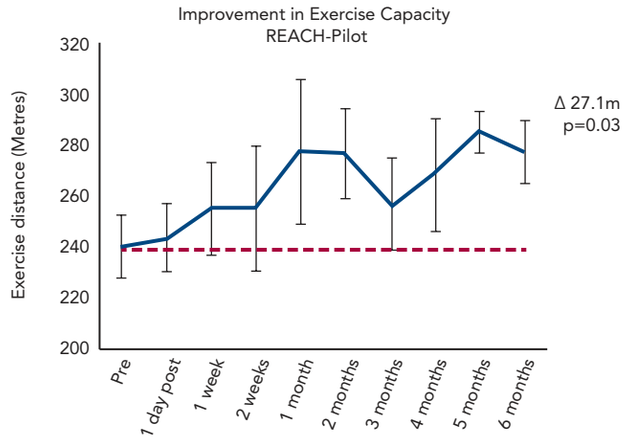
Schmieder, 2013,[48] reproduced from the EuroPCR presentation, slide 16. ABPM = ambulatory blood pressure monitoring; BP = blood pressure; mmHg = millimetres of mercury.

New Therapeutic Indications for Renal Denervation

Evolving applications for RDN in disease conditions related to sympathetic overactivity may expand its therapeutic indications. The sympathetic nervous system has an impact on a number of cardiovascular and metabolic diseases,[31] and possible indications for RDN include the treatment of glycemic control,[32] sleep apnoea,[32] cardiac systolic and diastolic dysfunction,[33,34] LVH,[33] polycystic ovary syndrome[34] and end-stage renal failure.[35]

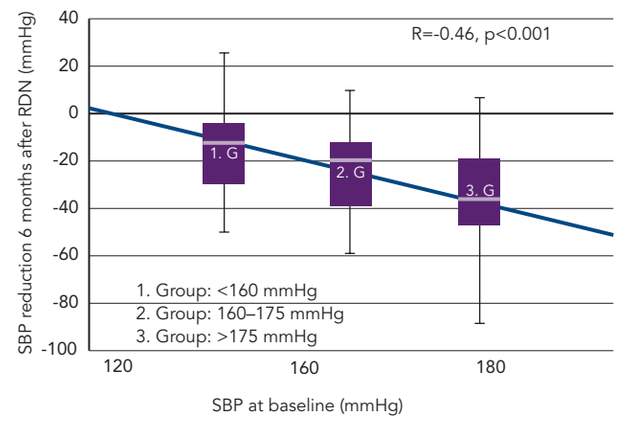
The mechanisms that underlie heart failure may also benefit from RDN. In congestive heart failure, sympathetic overactivation that accompanies decreased cardiac output causes renin release, sodium and fluid retention, and reduces renal blood flow, leading to arterial constriction and increased heart rate. An increase in plasma levels of angiotensin II, partly mediated by renal sympathetic activation, acts on the central nervous system to further increase global sympathetic tone.[36] Renal sympathetic activity causes norepinephrine activation; levels of plasma

Figure 4: Improvement in Exercise Capacity in Patients with Heart Failure Following Renal Denervation



Davies et al., 2013,[40] reproduced from slide 29 of the presentation.

Figure 5: Baseline Systemic Blood Pressure and Blood Pressure Reduction Following Renal Denervation



mmHg = millimetres of mercury; RDN = renal denervation; SBP = systolic blood pressure. Weil, 2013,[47] reproduced from the EuroPCR presentation, slide 8.

norepinephrine correlate with mortality in patients with congestive heart failure.[37] Two mechanisms are thought to be responsible for fluid retention – a slow renal mechanism and a faster pathway whereby the splanchnic venous reservoir becomes activated and blood becomes immobilised.[38]

Another clinical feature of heart failure is overactivation of central chemoreceptors, modulated by sympathetic pathways, which causes breathlessness. Chemoreceptor sensitivity increases with worsening heart failure and high chemoreceptor activation is associated with increased mortality.[39] Numerous effective drugs are available for the treatment of arterial constriction and diuretics can help in the management of fluid retention. However, there are few options for modifying the sensitivity of the chemoreceptors that control breathing. RDN offers the potential to modulate central chemoreceptors, improve fluid balance, reduce heart rate and cause a decrease in peripheral vascular resistance.

A small pilot study (n=7) assessed the safety of RDN in patients with chronic heart failure and on maximal tolerated heart failure therapy.[40] Patients were hospitalised for a day before the procedure and up to five days after, and were closely followed up. No procedural or post-procedural complications were observed during six months of follow-up. Improvements in both symptoms and exercise capacity were reported, and the resulting reduction in BP was negligible and remained stable. The six-minute walk distance was significantly increased at six months (Δ=27.1 ± 9.7 m, p=0.03), with each patient experiencing an increase (see *Figure 4*). The procedure also resulted in dose reduction in some medications, in particular diuretic dosage, which was reduced in four of the seven patients.

In a larger study of patients with advanced heart failure (n=51, 12 months), 26 patients were treated with RDN and standard pharmacotherapy and 25 patients received standard drug treatment with beta-blockers, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) and diuretics. No acute or medium term complications were observed in the RDN group. The RDN group reported an increase in ejection fraction, a lower cumulative frequency of hospitalisations for heart failure, and also showed other interesting trends, such as a reduction in the N-terminal pro-hormone of brain natriuretic peptide (NT proBNP), a reliable indicator of the severity of heart failure.[41]

Several ongoing studies aim to assess the safety and efficacy of RDN in heart failure. These include the SYMPLICITY-HF trial (n=40), and the Renal Artery Denervation in Chronic Heart Failure (REACH) trial (n=100). In summary, RDN may offer the potential to expand its indications beyond resistant hypertension.

Building a Successful Renal Denervation Referral Network

Following current consensus papers, around 10–15 % of current patients are suitable for RDN, and proper evaluation is important. Firstly, it is necessary to identify patients who have truly resistant hypertension, taking into account compliance issues. In patients with resistant hypertension, secondary causes of hypertension are common.[42] Therefore a detailed screening process is required to identify patients with potentially curable forms of hypertension, since RDN has not been evaluated for efficacy in these patients.[27]

Ultimately, the success of RDN rests on building a referral network. Evaluation of patients for secondary hypertension and end-organ damage often requires different specialists. A multidisciplinary team is therefore recommended, including hypertension experts, radiologists, nephrologists, endocrinologists and both interventional and non-invasive cardiologists to exclude secondary causes of hypertension and make the right decision for each individual patient.[43] The importance of the multidisciplinary approach has been stressed by hypertension experts and has proven successful in daily practice.[27,44] It is important to identify the referring physicians, which may be a family practitioner rather than a specialist. Involvement of local physicians can help to spread awareness and knowledge about the procedure.

In targeting appropriate patients for RDN, the new European Society of Hypertension (ESH) guidelines[45] are useful – office BP ≥160 mmHg systolic (diabetics ≥150 mmHg); a stable drug regimen including a diuretic and three different antihypertensive drugs and age over 18 years. Currently, the only parameter identified that predicts response to RDN is baseline SBP – a correlation has been demonstrated between BP reduction after RDN at six months follow-up and SBP baseline values (see *Figure 5*).[46]

The establishment of an RDN referral network maintains a streamlined patient evaluation. In a referral network established in Lubeck, Germany, 41 % of patients were excluded because they were taking less than three medications and 26 % were excluded because they had a SBP <160 mgHg. Twenty-six percent of all the patients seen were treated with RDN. The SBP at baseline was around 180 mmHg, the reduction in BP observed was about 26 mmHg. These real-world data are similar to those observed in clinical trials.[47]

In summary, patient selection is crucial to the success of a RDN programme. In order to optimise patient selection, it is important to build a multidisciplinary referral network by personal communication and quality of medical treatment.

Summary and Concluding Remarks

RDN using the Symplicity RDN system represents an exciting and innovative development in the field of interventional medicine. It has demonstrated significant and sustained reductions in BP in the Symplicity HTN-1 and Symplicity HTN-2 clinical trials. The Global SYMPLICITY Registry has also demonstrated safety and effectiveness in real-world clinical practice in the subjects for which data are available. New systems containing multi-electrodes has the potential to make RDN as easy and straightforward as the existing single-electrode catheter while reducing ablation time. Furthermore, the benefits of RDN may not be restricted to blood pressure lowering alone; the potential exists to expand its therapeutic indications. However, RDN is a relatively new technique and optimal patient selection is crucial. The joint expertise of different fields is required to identify patients who have truly resistant hypertension and are likely to respond to RDN. Clinical evidence to date suggests that a high baseline SBP is the best predictor of response. In conclusion, RDN is currently an effective and safe option if used in well-selected patients. As more clinical data become available, the approach to RDN is likely to become more accessible with an increase in indications. ■

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