Catheter-based renal denervation for treatment of resistant hypertension

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ABSTRACT

INTRODUCTION: Activation of renal sympathetic nerves is associated with the development of hypertension. Catheter-based renal sympathetic denervation with radiofrequency energy ablation is a new promising treatment option for resistant hypertension. We here report the first Danish experiences and results with this technique.

MATERIAL AND METHODS: Nine patients with resistant hypertension and a day-time 24-hour ambulatory blood pressure (BP) of 152/89 mmHg ± 10/10 (standard deviation) mmHg despite treatment with 5.4 ± 1.4 anti-hypertensive drugs underwent catheter-based renal sympathetic denervation with the Symplicity catheter.

RESULTS: No periprocedural complications or adverse events during follow-up were observed. Seven patients received complete ablation and two patients only partial ablation. Five patients responded to the treatment with a reduction in day-time 24-hour ambulatory BP from 158/94 ± 13/9 mmHg to 139/82 ± 10/8 mmHg ($p < 0.05$) at the one month follow-up and a reduction in the number of antihypertensive drugs from 5.4 ± 1.6 to 3.4 ± 0.9 ($p < 0.05$). BP in the remaining four patients was not significantly changed and antihypertensive therapy was not changed.

CONCLUSION: Catheter-based renal sympathetic denervation is a feasible and in several cases also effective treatment option for patients with resistant hypertension. Adequately designed controlled trials are needed to assess the long-term safety and the full potential of this treatment.

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Hypertension affects approx. 30% of the adult population in Denmark. The condition is under-diagnosed and also under-treated and remains a major cause of cardiovascular morbidity and mortality [1].

Despite the availability of numerous effective antihypertensive agents, adequate blood pressure (BP) control is not achieved in a large number of subjects. Although several patient- and physician-related aspects contribute to this problem, it is not unusual that even treatment with multiple antihypertensive agents fails to lower the BP to the recommended values, i.e. patients with resistant hypertension. It is estimated that these patients comprise around 10% of the hypertensive population [2].

Increased activity in the sympathetic nervous system is recognized as an important contributor to the development and progression of hypertension [3]. In particular, renal sympathetic activation results in increased renin secretion, enhanced sodium reabsorption and renal vasoconstriction, all of which contribute to increase BP [4]. Historically, surgical sympathectomy was successful in lowering the BP in patients with severe hypertension [5]. However, this approach was associated with a high perioperative morbidity and mortality and with long-term complications and was abandoned with the advent of modern antihypertensive drug therapy.

Sympathetic nerves enter the kidneys in the walls of the renal arteries and lie within reach of radiofrequency energy delivery. In recent years, the advent of a catheter-based technique using radiofrequency energy to ablate the renal sympathetic nerves (**Figure 1**) has reintroduced renal denervation to the treatment of hypertension. It was demonstrated that the technique is safe and effective in lowering BP in a randomized trial in patients with resistant hypertension [6].

We here report the first Danish experiences and results with the technique.

MATERIAL AND METHODS

Patients

Individual patient data are shown in **Table 1**. Patients were eligible if they had a systolic daytime 24-hour ambulatory BP of 135 mmHg or more despite being treated with at least three antihypertensive drugs including a diuretic, or confirmed intolerance to medication. The renal artery anatomy was evaluated by a computer tomography (CT) angiogram and considered suitable in case of a vessel diameter of ≥ 4 mm, no significant stenosis or other abnormalities.

Patients were not eligible in case of pregnancy, age below 18 years, any known secondary cause of hypertension, or an estimated glomerular filtration rate below 45 ml/min. Excluded from the intervention were also patients with a left ventricular ejection fraction below 50%, recent myocardial infarction or percutaneous coronary intervention, significant proximal coronary artery stenosis or haemodynamically significant valvular heart disease.

ORIGINAL ARTICLE

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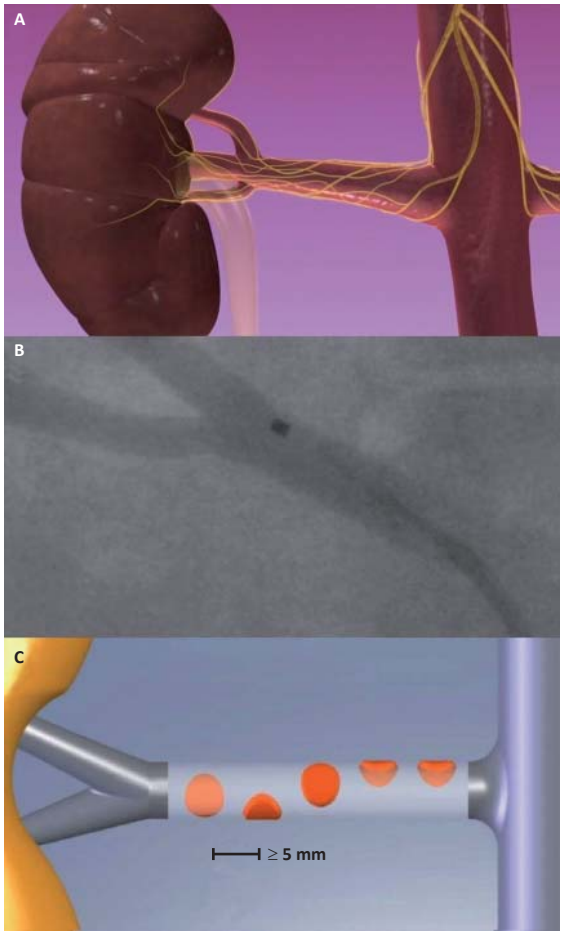
FIGURE 1



A. The renal sympathetic nerves located in the adventitia of the renal artery. **B.** Fluoroscopy image of the Symplicity ablation catheter in the right renal artery. **C.** Spiral-shaped ablation pattern along the renal artery. Modified from Symplicity Educational Material (Medtronic, Santa Rosa, CA, USA).

Procedure

Using local anaesthetics, cannulation of the femoral artery was performed by direct puncture. A 6Fr sheath was introduced and unfractionated heparin administered using an intravenous bolus of 70 IE/kg bodyweight with a target-activated clotting time (ACT) > 250 s. Initially, a coronary angiogram was obtained using standard technique to exclude significant proximal coronary artery stenosis. Using a 6Fr renal double curve (RDC) or a left internal mammary artery (LIMA) guiding catheter, an angiogram of the renal arteries was recorded and the Symplicity (Medtronic, Santa Rosa, CA, USA) steerable radiofrequency catheter was introduced into the renal artery. The tip of the catheter was positioned under fluoroscopic guidance to make close contact with the vessel wall. Discrete RF ablations (of approximately 8 watts) lasting 2 minutes each were applied in order to achieve four to six ablations separated both longitudinally and circumferentially within each renal artery (Figure 1).

A control angiography was performed after the procedure. Periprocedural pain associated with delivery of RF energy was managed by intravenous midazolam and fentanyl. Patients were discharged from hospital the day after the procedure. Follow-up was performed at one month (or earlier if needed) with ambulatory 24-hour BP measurement and assessment of clinical status.

Statistical analysis

Statistical analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL).

All estimates are given as means ± standard deviation, unless otherwise stated.

Paired-samples t test was used. The level of significance was $p < 0.05$.

Trial registration: not relevant.

RESULTS

Patient characteristics are shown in **Table 2**. The procedure time (i.e. from puncture of the femoral artery to closure) was 57 ± 15 minutes. The mean fluoroscopy time was 14 ± 3 minutes, and 124 ± 36 ml contrast (Visipaque) was used.

The procedure was successfully performed with application of 4.7 ± 1 ablations per renal artery in seven of the nine patients. Two patients received only partial ablation due to renal artery spasm refractory to intra-arterial infusion of nitroglycerine (patient no. five) and the unexpected finding of dual renal arteries (with a severe stenosis in one of these) to the right kidney (patient no. nine). No adverse events were recorded during or after the procedure which was well tolerated by the patients who experienced minor or no discomfort.

In five patients, the antihypertensive therapy was partly discontinued during the first four weeks after the catheter-based renal denervation (RDN) due to hypotension or hypotensive symptoms, and this subgroup exhibited marked reductions in day-time 24-hour ambulatory BP from 158/94 ± 13/9 mmHg to 139/82 ± 10/8 mmHg ($p < 0.05$), while the antihypertensive therapy was reduced from 4.4 ± 1.6 to 3.4 ± 0.9 ($p < 0.05$) different drugs daily.

24-hour ambulatory daytime BP and antihypertensive therapy before and one month after RDN are shown in Table 1 and **Figure 2**. The overall reductions in systolic and diastolic pressures of 7 ± 15 mmHg and 6 ± 13 mmHg, respectively, and the reduction in antihypertensive drugs of 1.1 ± 1.4 or expressed as daily defined doses (DDD) of 4.1 ± 7.6 were not statistically significant.

Renal function assessed by plasma levels of creatinine and estimated glomerular filtration rate was unchanged by the procedure (79 ± 20 mikromol/l versus

TABLE 1

Daily antihypertensive therapy and 24-hour ambulatory daytime blood pressure before and one month after renal denervation.

	Before RDN		1 month after RDN	
	antihypertensive therapy	24-h ambulatory daytime BP, mmHg	antihypertensive therapy	24-h ambulatory daytime BP, mmHg
Patient 1	Furosemide 750 mg	181/101	Furosemide 80 mg	145/80
	Spironolactone 200 mg		Amiloride 20 mg	
	Metoprolol 150 mg		Spironolactone 50 mg	
	Losartan 100 mg		Metoprolol 100 mg	
	Minoxidil 30 mg		Losartan 100 mg	
	Bendroflumethiazide 2.5 mg			
Patient 2	Terazosin 2 mg	148/93	Losartan 100 mg	128/76
	Losartan 100 mg		Amiloride 15 mg	
	Amiloride 20 mg		Eplerenone 50 mg	
	Eplerenone 50 mg		Bendroflumethiazide 2.5 mg	
	Bendroflumethiazide 2.5 mg			
Patient 3	Amlodipine 5 mg	164/104	Amlodipine 5 mg	155/93
	Losartan 150 mg		Losartan 150 mg	
	Bendroflumethiazide 1.25 mg		Bendroflumethiazide 1.25 mg	
Patient 4	Bendroflumethiazide 2.5 mg	139/81	Bendroflumethiazide 2.5 mg	146/83
	Enalapril 30 mg		Enalapril 30 mg	
	Losartan 100 mg		Losartan 100 mg	
	Amiloride 20 mg		Amiloride 20 mg	
Patient 5	Moxonidine 0,4 mg	162/101	Moxonidine 0.4 mg	174/109
	Furosemide 40 mg		Furosemide 40 mg	
	Metoprolol 100 mg		Metoprolol 100 mg	
	Ramipril 10 mg		Ramipril 10 mg	
	Terazosin 4 mg		Terazosin 4 mg	
Patient 6	Minoxidil 15 mg	153/95	Minoxidil 10 mg	136/90
	Furosemide 120 mg		Furosemide 60 mg	
	Metoprolol 200 mg		Ramipril 10 mg	
	Amlodipine 10 mg		Losartan 50 mg	
	Ramipril 10 mg			
	Irbesartan 300 mg			
	Hydroclorothiazide 12.5 mg			
Patient 7	Doxazosin 4 mg	142/76	Doxazosin 4 mg	150/79
	Bendroflumethiazide 2.5 mg		Bendroflumethiazide 2.5 mg	
	Spironolactone 25 mg		Spironolactone 50 mg	
	Carvedilol 25 mg		Carvedilol 25 mg	
	Felodipine 5 mg		Felodipine 10 mg	
	Losartan 50 mg		Losartan 100 mg	
Patient 8	Losartan 100 mg	146/79	Losartan 100 mg	133/75
	Atenolol 100 mg		Atenolol 100 mg	
	Furosemide 40 mg			
	Moxonidine 0.4 mg			
	Lercanidipine 10 mg			
Patient 9	Furosemide 90 mg	143/83	Furosemide 90 mg	144/72
	Bisoprolol 10 mg		Bisoprolol 10 mg	
	Lercanidipine 10 mg		Lercanidipine 10 mg	
	Ramipril 10 mg		Ramipril 10 mg	
	Candesartan 32 mg		Candesartan 32 mg	
	Spironolactone 100 mg		Spironolactone 100 mg	

BP = blood pressure; RDN = renal denervation.

74 ± 25 mikromol/l and 78 ± 13 ml/min versus 79 ± 17 ml/min, respectively).

Several patients (no. 1, 6 and 8) reported dramatic symptom relief (from daily headache and fatigue) and improvements in quality of life after the procedure.

DISCUSSION

Our first experience with catheter-based renal sympathetic denervation is in line with the recent proof of concept trial [7] and the first randomized trial [6], and it demonstrates the safety and in several patients also

the efficacy of this new treatment modality in daily clinical practice for patients with treatment-resistant hypertension.

Marked reductions in BP and the intensity of antihypertensive drug therapy were achieved in five of the nine patients, but overall the changes were not significant. The limited patient number and the lack of complete ablation in two patients are likely contributing explanations for this fact. We also measured the effect of RDN on 24-hour ambulatory BP and not-clinic BP, as 24-hour ambulatory BP more accurately predicts the risk of cardiovascular morbidity and mortality [8]. The only data available on the effect of RDN on 24-hour ambulatory BP measurements stems from a subgroup of patients in the randomized trial by Esler and colleagues [6]. Here, significant reductions of 11 ± 15 mmHg systolic and 7 ± 11 mmHg diastolic were reported – a considerably smaller effect than the reductions in clinic BP of 32 ± 23 mmHg systolic and 12 ± 11 mmHg diastolic. Furthermore, we measured the BP after one month, but it seems that the complete effect of RDN is achieved at six months, as (clinic) BP was reduced by 20 ± 21 mmHg systolic and 7 ± 8 mmHg diastolic in the before-mentioned trial after one month [6] compared with the six-month values stated above.

Not every patient can be expected to respond to the treatment. Esler and colleagues reported a 16% non-response rate (when response was defined as a reduction in systolic BP of 10 mmHg or more), but the true non-response rate is undoubtedly higher as it was not a double-blinded study and as variations in BP (biological and measurement-related) will lead to misclassification of some of the true non-responders. This is confirmed by the control group of that study which had a 35% response rate despite no active treatment [6]. It may be hypothesized that the reason for the lack of response is a result of incomplete ablation of the renal sympathetic nerves and/or the fact that renal sympathetic nerves are not equally important in the pathophysiology behind the BP elevation in all patients. At present, no periprocedural monitoring for evaluation of the completeness of ablation exists, and it is unknown whether a patient with no BP reduction after RDN should be offered a second procedure. Further research is also warranted to determine the patient selection methods most likely to identify patients who will respond to treatment.

Overall, the reduction in blood pressure was not significant, but our results support that at least in some patients, RDN leads to a marked and otherwise unachievable lowering of blood pressure. Along with the first (and so far only) randomized and controlled trial [6], our results may, however, be biased by an increased patient compliance regarding ingestion of antihypertensive medication after RDN. This emphasizes the need for confirmation of the effect of RDN in a double-blinded randomized and controlled trial. Such a trial has recently been initiated at Aarhus University Hospital, Skejby (ClinicalTrials.gov Identifier: NCT01459900).

Before RDN, several patients suffered from symptoms, particularly headache and fatigue. These symptoms were very likely related to the elevated BP or they were adverse effects of the antihypertensive therapy. Interestingly, three patients experienced massive symptom relief and improvement in quality of life after the procedure along with reductions in BP and the intensity of their antihypertensive therapy. No randomized and blinded data are yet available on this issue, but the potential effect of RDN on symptoms and on quality of life seems a relevant and exiting aspect that should be further explored in a randomized and blinded controlled trial.

Along with efficacy, safety remains an equally important issue in a therapy targeting risk reduction for cardiovascular morbidity and mortality. No adverse events were noted in our patient population periprocedurally and/or at one month follow-up. In the first proof-of-principle study, no renal artery stenosis occurred (evaluated by renal magnetic resonance imaging angiogram at six months) [7]. To our knowledge, among all patients treated worldwide, only local dissection of the renal artery without sequelae was noted during the procedure in one patient [7], and in another patient, possible progression of an underlying atherosclerotic lesion was identified, but required no intervention [6].

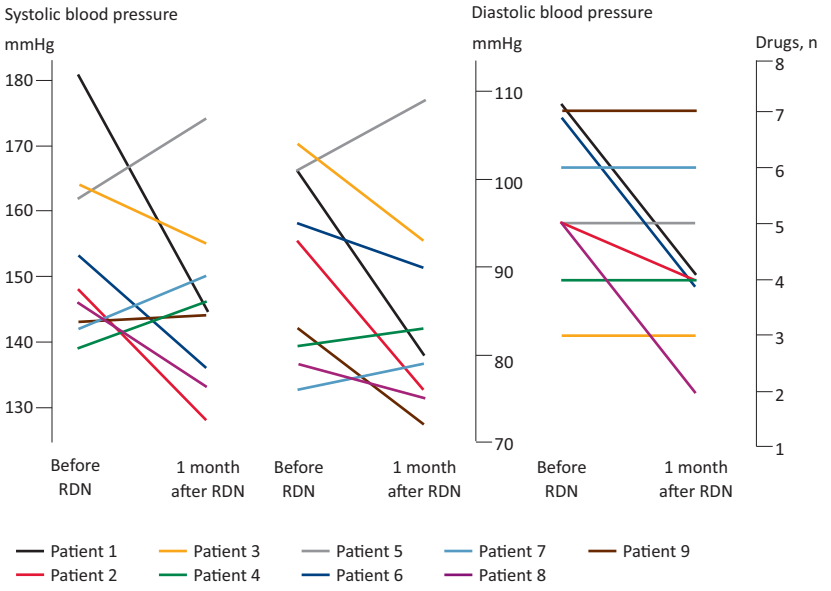
TABLE 2

Baseline characteristics of the nine patients with treatment-resistant hypertension. Values are means ± standard deviation or absolute numbers (percentages).

Age, years	56 ± 10
Gender, female	6 (67)
Body mass index kg/m^2	27.5 ± 4.7
P-creatinine, µmol/l	79 ± 20
Estimated GFR, ml/min	78 ± 13
Target organ damage	
Albuminuria	4 (44)
Left ventricular hypertrophy	3 (33)
Medical history	
Coronay artery disease	1 (11)
Cerebrovascular disease	2 (22)
Diabetes	2 (22)
24-hour day-time ambulatory systolic BP, mmHg	152 ± 10
24-hour day-time ambulatory diastolic BP, mmHg	89 ± 10
24-hour night-time ambulatory systolic BP, mmHg	140 ± 13
24-hour night-time ambulatory diastolic BP, mmHg	81 ± 11
Antihypertensive medications	5.4 ± 1.4
Antihypertensive therapy in daily defined doses	11 ± 7

BP = blood pressure; GFR = glomerular filtration rate.

FIGURE 2



24-hour ambulatory daytime blood pressure and number of antihypertensive drugs before and after the catheter-based renal denervation (RDN).

No long-term adverse events have been reported. Considering the physiological effects of the renal sympathetic nerves, it may be speculated that after RDN patients will be more vulnerable to sodium depletion and/or conditions with haemodynamic compromise, particularly hypovolaemia. This issue remains to be settled, however the cardiovascular response to exercise is unchanged after RDN [9] and arterial baroreflex function is improved [10], suggesting an intact cardiovascular regulation.

Pathophysiological proof of concept of the RDN has been shown in a small subset of patients with reductions in renal norepinephrine spill over rates of 47%, implying disruption of efferent sympathetic nerve traffic [7]. Interestingly, sympathetic outflow to the rest of the body is reduced as well (evaluated by microneurography) [10]. The likely mechanism is disruption of the afferent renal nerves that have been demonstrated to stimulate central sympathetic activity [11].

Generalized reduction in sympathetic nerve activity is a very promising effect of RDN and expands the potential benefits of RDN to a magnitude of conditions associated with sympathetic over activity – heart failure, arrhythmias, chronic kidney disease, obstructive sleep apnoea etc. Generalized reduction in sympathetic nerve activity is also beneficial with respect to glucose metabolism, and indeed reductions in fasting glucose levels and insulin resistance have already been reported after RDN [12].

In conclusion, RDN is a feasible and effective addition to the therapeutic arsenal in the treatment of hypertension and seems safe although long terms effects are unknown. It is still at a very early stage of clinical application and for now limited to resistant hypertension. Adequately designed controlled trials are needed to assess the long term safety and full potential of RDN.

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