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Case Report

Catheter-Based Renal Sympathetic Denervation for the Treatment of Resistant Hypertension: First Experience in Greece with Significant Ambulatory Blood Pressure Reduction

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We describe the first two cases in Greece of catheter-based renal sympathetic denervation (RSD) by means of radiofrequency ablation. The procedure was performed on middle-aged men with long-standing resistant hypertension (office blood pressure, BP 195/115 mmHg and ambulatory BP 190/110 mmHg; office BP 170/95 mmHg and ambulatory BP 151/87 mmHg) under optimal medical therapy. The percutaneous RSD was completed successfully, and led to a significant reduction in both office and ambulatory BP at 3 weeks, with no vascular complications, while renal function remained unaltered. These cases of RSD suggest that renal nerve ablation for the treatment of resistant hypertension constitutes an effective and safe therapeutic modality, accompanied by significant reduction of ambulatory BP, and broadening of its clinical use in our country is of clinical importance.

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It is currently established that the sympathetic nervous system participates in the complex pathophysiology of blood pressure (BP) regulation in humans, while renal sympathetic overdrive constitutes a major characteristic of hypertension.[1-3] Percutaneous catheter-based techniques that can induce renal sympathetic denervation (RSD) by radiofrequency ablation are emerging as a viable and safe approach to achieve sustained BP reduction in patients with resistant hypertension.[1-6] We describe the first cases in Greece of middle-aged male patients with resistant hypertension who successfully underwent percutaneous RSD, performed using the commercially available Symplicity catheter, with a significant reduction of BP at 3 weeks' follow up. We also provide a brief description of the denervation procedure and discuss the currently available data on the efficacy of RSD.

Case presentation

The first case was a 58-year-old man, type 2 diabetic, dyslipidemic with a history of coronary artery disease (obstruction in the distal section of the left anterior descending with collaterals from the right coronary artery) and peripheral arterial disease (left carotid revascularization 5 years earlier), who was referred to our outpatient hypertensive unit for further evaluation and treatment. He presented with long-standing essential hypertension that was resistant to pharmacologic therapy with 8 different antihypertensive drugs, including a thiazide diuretic at maximal tolerated doses. Confirmation of hypertension was based on 3 outpatient measures with mean office BP 195/115 mmHg and ambulatory BP 190/110 mmHg with absence of dipping status (Table 1). The second case was a 66-year-old man, free of coronary artery and peripheral artery disease, with hypertension resistant to 6 antihypertensive drugs. In this patient, diagnosis of his hypertensive status was based on outpatient measures of mean office BP 170/95 mmHg and ambulatory BP 151/87 mmHg with a non-dipping profile (Table 1). Additionally, both patients underwent the recommended clinical and laboratory workup in order to rule out secondary forms of hypertension.[7]

Regarding the hypertensive target organ in the first patient, he exhibited left ventricular hypertrophy (left ventricular mass index 138 g/m^2) with an ejection fraction of 50%, microalbuminuria (albumin to creatinine ratio 55 mg/g), moderately impaired renal function with an estimated glomerular filtration rate (MDRD formula) of 58 ml/min/1.73 m^2, and finally fundoscopy revealed hemorrhages and exudates. The second hypertensive patient also had left ventricular hypertrophy (left ventricular mass index 136 g/m^2) with 65% ejection fraction and preserved renal function (73 ml/min/1.73 m^2).

Given the uncontrolled nature of the resistant hypertension and progression of target organ damage, both patients were eligible for percutaneous RSD.[5,6] Towards this end, computed tomography was performed for detailed evaluation of renal artery anatomy. Patients had no multiple main renal arteries, no significant atherosclerotic lesions/stenoses, and had bilateral renal artery length >20 mm and lumen diameter >4 mm, enabling the catheter-based RSD to be performed.

Under local anesthesia, a 6 French introducer sheath was inserted into the femoral artery using the standard percutaneous technique (modified Seldinger). A heparin bolus of 3000 to 5000 units was then administered intravenously. A 6 French right Judkins catheter was inserted to engage the main renal artery sequentially and nitroglycerin was injected directly to the artery to avoid spasm. Images of the main left and right renal arteries were recorded using a non-ionic contrast in order to further assess anatomy and dimensions. Then the specially designed and commercially available radiofrequency ablation catheter (Symplicity, Ardian, Medtronic) engaged the left main renal artery and the tip was positioned proximal to the bifurcation of the left main renal artery under fluoroscopy (Figure 1). Before initiation of the RSD, patients were given morphine intravenously to decrease the pain during the radiofrequency delivery procedure. After injection of intrarenal nitroglycerin, by rotating and angulating the catheter's tip the site of initial ablation was chosen, the impedance, temperature and resistance were measured, and radiofrequency energy was delivered according to a pre-specified protocol, lasting up to 2 minutes and of 8 watts or less. (Figure 2). Then the catheter was withdrawn proximally and another 7 successive discrete ablations, separated both longitudinally and rotationally within the artery, were applied. The ablation was performed in a similar fashion in the right renal artery

Table 1. Blood pressure data before and 3 weeks after renal sympathetic denervation in our two patients with resistant hypertension.

Parameter	Before RSD 1st case	Before RSD 2nd case	3 weeks after RSD 1st case	3 weeks after RSD 2nd case
Office SBP (mmHg)	195	170	150	145
Office DBP (mmHg)	115	95	90	90
Office HR (bpm)	70	65	68	60
Home SBP (mmHg)	180	150	150	140
Home DBP (mmHg)	105	95	90	85
Home HR (bpm)	70	60	65	60
24-h SBP (mmHg)	190	151	143	138
24-h DBP (mmHg)	110	87	88	81
24-h HR (bpm)	67	57	57	56
Daytime SBP (mmHg)	194	154	147	141
Daytime DBP (mmHg)	116	90	91	84
Daytime HR (bpm)	71	58	61	55
Nighttime SBP (mmHg)	180	144	136	130
Nighttime DBP (mmHg)	97	80	82	72
Nighttime HR (mmHg)	58	54	50	52

SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate; RSD – renal sympathetic denervation

Figure 1. Fluoroscopic image in anterior-posterior projection of the radiofrequency renal sympathetic denervation ablation catheter engaged in the left main renal artery with the tip positioned proximal to the bifurcation.

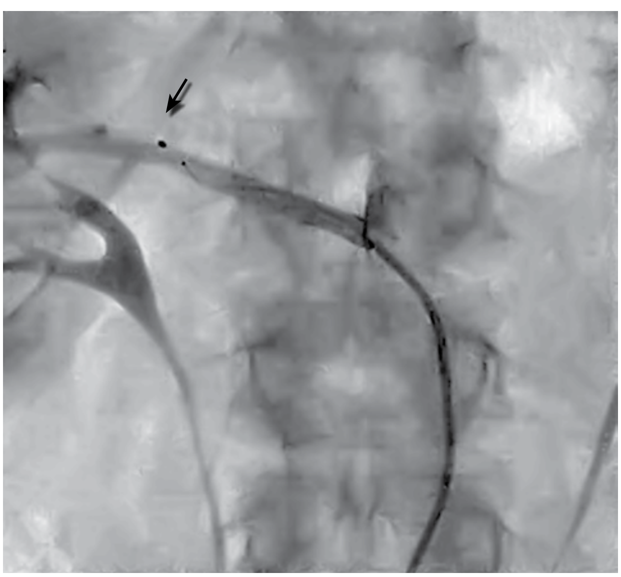

Figure 2. The tip of the renal sympathetic denervation catheter rotated and angulated at the site of the initial ablation, with positioning to ensure appropriate impedance, temperature and resistance for successful radiofrequency energy delivery according to a pre-specified algorithm

and when the procedure was completed the catheter was removed, with the time from the first to the last radiofrequency ablation being 42 minutes in the first case and 38 minutes in the second. No signs of renal artery abnormalities (vasospasm, stenosis or dissection) were apparent after non-ionic contrast injection.

After the completion of the RSD, both patients were transferred to the recovery unit, the sheath was removed and the femoral artery was manually compressed to achieve hemostasis. The patients felt no discomfort after the procedure and their BP and heart rate levels were comparable to those before the procedure. After hospitalization for 24 hours no complications of vascular origin or serum creatinine levels deteriorations were observed. The patients were advised to continue their medication as before RSD, with the exception of lowering the dose of hydrochlorothiazide from 25 mg/day to 12.5 mg/day, and to measure home BP regularly according to guidelines.[7] Blood sampling and 24-h ambulatory BP monitoring were scheduled after 3 weeks. Interestingly, at the follow up of 3 weeks the first patient reported home BP levels of 145/85 mmHg without the usual surge in the morning hours. This significant reduction in hemodynamic load was confirmed by the ambulatory BP measurements, with a mean 24-h level of 143/88 mmHg (Table 1). Along the same lines, office BP measurements were 150/90 mmHg during the visit at 21 days. The second patient reported a home BP of 140/85 mmHg, ambulatory BP 138/81 mmHg and office BP 145/90 mmHg. Regarding the biochemical profile the patients exhibited unaltered glucose, lipid levels, electrolytes, as well as renal function assessed by serum creatinine and estimated glomerular filtration rate (Table 2). Based on the above, both patients were advised to continue current antihypertensive treatment and to visit our outpatient hypertensive unit on a monthly basis for further clinical monitoring and therapeutic management.

Discussion

The first report on surgical sympathectomy to reduce BP in severely hypertensive patients, given the lack of appropriate drug treatment, dates back to 1935.[8] However, this surgical technique, although successful in controlling BP and prolonging survival, exhibited significant and not easily tolerated side-effects.[8,9] Nowadays, catheter-based RSD by means of radiofrequency ablation has been shown to reduce BP and alleviate the sequelae of hypertension via interference with both efferent and afferent sympathetic nerves and potentially further central mechanisms.[1,4-6,10] The most important clinical data are derived from the Symplicity HTN-2 trial, a multicenter, prospective, randomized controlled trial that included patients with baseline systolic BP of 160 mmHg or more (≥150

Table 2. Laboratory data before and 3 weeks after renal sympathetic denervation in our two patients with resistant hypertension.

Parameter	Before RSD 1st case	Before RSD 2nd case	3 weeks after RSD 1st case	3 weeks after RSD 2nd case
Glucose (mg/dl)	88	85	86	84
Urea (mg/dl)	42	38	48	40
Serum creatinine (mg/dl)	1.3	1.02	1.3	1
eGFR (ml/min/1.73 m^2)	58	73	58	75
Uric acid (mg/dl)	6.2	5.4	6	5
Potassium (meq/L)	3.5	3.8	4.1	4
Sodium (meq/L)	137	139	142	144
Total cholesterol (mg/dl)	141	138	151	140
Triglycerides (mg/dl)	121	118	126	112
HDL-cholesterol (mg/dl)	35	37	38	39
LDL-cholesterol (mg/dl)	82	77	88	82

eGFR – estimated glomerular filtration rate; HDL – high-density lipoprotein; LDL – low-density lipoprotein; RSD – renal sympathetic denervation

mmHg in patients with diabetes mellitus 2) randomly assigned to RSD (with the same radiofrequency catheter used in our case) in conjunction with medical therapy or medication alone (control group). In the RSD group of 52 patients, office BP drop was evident as early as 1 month post-procedure and a statistically significant decrease of 32/12 mmHg was present at 6 months, whereas in the control group no changes in BP were observed.[6] In our cases the drop in office systolic/diastolic BP was 45/25 mmHg in the first patient and 25/5 mmHg in the second one, in line with the results of the Symplicity HTN-2 trial. Most importantly, office BP blunting was confirmed by ambulatory measurements in these first cases in our country, strengthening the efficacy of the procedure in terms of a sustained reduction of hemodynamic load over 24-hours. Moreover, a longer follow up in resistant hypertensive patients after RSD showed a reduction of 32/14 mmHg at 24 months, underscoring the durability of BP control with this denervation method.[11] Whether in our patient the promising results regarding BP control by RSD will pass the test of time remains to be determined with a longer follow up. It is of note that no serious procedure-related complications were observed in the abovementioned trials, as in our cases, although there are still limited concerns about longer-term safety and efficacy.[9]

Apart from the established effect of RSD on hemodynamic load, interruption of renal sympathetic innervation has been documented to positively affect glycemic status.[12] Data from a recent study showed that catheter-based RSD substantially improved insulin sensitivity and glucose metabolism, in addition to significantly reducing BP.[12] Since hypertension is present in the majority of patients with chronic and end-stage renal failure and sympathetic overactivity is a hallmark in patients with chronic renal disease, this catheter-based technique may also be used in such patients.[13,14] Indeed the first report orientated in this direction presented a 36-year-old male patient with end-stage renal disease caused by a hereditary Alport syndrome and drug resistant hypertension.[13] The patient underwent RSD and exhibited a reduction in 24-h ambulatory BP of 10/10 mmHg at 1 month and of 76/51 mmHg at 3 months, with stable diuresis, establishing the basis for a clinical trial in the setting of renal failure.[13]

Adding further evidence to the multifaceted beneficial effects of catheter-based RSD, in patients with refractory hypertension and obstructive sleep apnea, apart from BP control, RSD is associated with an improvement of sleep apnea severity and unexpected improvements in glucose tolerance.[15] Finally, RSD improves the cardiopulmonary response to exercise by decreasing exercise BP, reducing heart rate at rest, and ameliorating its recovery without compromising chronotropic competence.[16]

Regarding all the above diverse effects of RSD beyond BP control in our cases, no exercise testing data are available and we observed no changes in renal function and glucose levels. This may be due to the short follow-up period, which limits our clinical insight into these parameters potentially influenced by the procedure with the course of time. Furthermore, novel techniques, such as the chemical ablation of the renal sympathetic fibers, provided promising results in a recent animal study.[17]

In conclusion, these are the first two cases of successful catheter-based RSD in Greece, demonstrating that renal nerve ablation for the treatment of hypertension constitutes an effective and safe therapeutic choice accompanied by significant reduction in ambulatory BP. Broadening of its clinical use in our country is thus of clinical importance. This is made even more evident by the pleiotropic effects of RSD, apart from BP control, which suggest a wider spectrum of applications for this novel method, from the milder forms of hypertension to chronic kidney disease and congestive heart failure.

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