A Complicated Case of Resistant Hypertension

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Abstract- A 47-year-old woman presented with a history of resistant arterial hypertension, associated with disabling headache. She was subjected to an enormous number of tests in order to identify an underlying cause of secondary hypertension, such as pheochromocytoma or Cushing syndrome, but all the most common causes of secondary hypertension were investigated and gradually excluded. Factitious use of amphetamine or cocaine was excluded, and therapy compliance was verified by witnessed ingestion of drug therapy, in order to rule out Munchausen syndrome. The patient underwent a first transcatheter renal denervation (RDN) with poor effect on blood pressure (BP) at long term follow up. Because of extremely poor control of BP values, a second RDN was performed two years later, again with inadequate long term efficacy. Despite an uncontrollable pre-procedural BP, RDN had an excessive BP lowering effect in this patient, but only for few months. In conclusion, a definitive diagnosis was not performed in our patient, despite an extremely deepened examination of the most common cause of refractory hypertension.
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Keywords: Hypertension; Refractory hypertension; Renal denervation

Introduction

Resistant hypertension (RH), a clinical condition in which patients cannot control their BP despite the use of a diuretic and at least two other drugs with the complementary mechanism of action, (1) is a relatively common problem in developed countries. Indeed, about 10% of all hypertensive patients in the USA are affected by RH (2). Among higher risk populations (e.g. diabetes mellitus, obesity and chronic renal disease) the proportion of uncontrolled patients is even higher (3). New devices-related treatment for patients with RH was born, but they are not risk-free. Thus, a meticulous investigation of the patient is extremely important, in order to identify those who could obtain a benefit by these invasive procedures without an elevated risk of their drawbacks. We report a case of a patient with idiopathic and uncontrolled RH despite the use of optimal medical therapy and double renal denervation (RDN).

Case Report

Our patient, D. B. (who provided written consent for this case report) is a short (body mass index 27.5 kg/m^2) 47-year-old Caucasian woman, who was normotensive until 40-year-old. She is known for Reynaud phenomenon and familiarity for essential hypertension, but not for cerebrocardiovascular disease. Hypertension was diagnosed in 2007; by that time, her BP values progressively rise, until the patient presented in January 2012 in ER with an occipital and supraorbital headache and an arterial BP of 215/105 mmHg. After this hypertensive crisis, her BP measured at the office (4) was noted to be consistently elevated in the range of 180/100 mmHg on three occasions. Therefore, her therapy was potentiated, and she started treatment with telmisartan, nebivolol, amlodipine, and hydrochlorothiazide. In March 2012 she came to ER for a new hypertensive crisis (BP 220/100 mmHg) despite a new upgrade of her therapy (Figure). She was admitted to our hospital, and she was tested for the most common causes of secondary hypertension: renin activity and aldosterone values were within normal range; renal arteries Duplex-Doppler study ruled out renal arteries stenosis; metanephrine, normetanephrine, and 24-hour urinary catecholamines were also in the normal range. There were no differences in BP values between lower and upper extremities. Aortic coarctation, renal parenchymal disease, and Cushing syndrome were also ruled out using abdomen ultrasound and thoracic and abdominal thin-slice computer tomography, while

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encephalic MRI allowed excluding hypophysis pathologies. Last, 24-hour urinary collection of drug metabolites such as cocaine or amphetamine was always unremarkable (Table 1). In consideration of her high BP values, measured also with 24-hour BP monitoring (180/100 mmHg), she was also tested for organ damages, without any pathologic findings (Table). Her fundus oculi revealed a normal arterial microcirculation, and no pathologic findings resulted from echocardiogram, supra-aortic branches, and renal arteries echo-doppler studies or encephalic and abdomen MRI. More than one urinalysis was performed, always without detection of proteinuria, and no electrolytes alteration was found in the 24-hour specimen. Antihypertensive therapy was further increased to the maximum tolerated posology of telmisartan and nebivolol, with canrenone in addition to the old therapy regimen (Figure).

In June 2012, because of evidence of refractory and uncontrolled hypertension, she had admitted again to our hospital for RDN, done with the Ardian Symplicity device (Medtronic Inc., Minneapolis, USA). The procedure was performed with apparently acute optimal and encouraging results (invasive arterial BP measurement on therapy during the procedure: 160/100 mmHg; 24-hour BPM at discharge: 100/60 mmHg) (Table 1). After the RDN she complained about palpitation and collapse due to orthostatic hypotension, and she was discharged with only propranolol, in order to control her reflex tachycardia (Figure). During the following summer months, her BP values were well controlled, with even some episodes of collapse for low BP (Figure). However, long term results of the RDN were disappointing: at the beginning of the cold season her BP values raised again, usually with peaks in the afternoon, and her therapy was gradually improved again, until February 2013, when she came to ER for a new hypertensive crisis (210/120 mmHg). She was hospitalized to retest contingent organ damages and to upgrade her therapy (Table). At that time, a self-blood pressure measurement (S-BPM) at home was recommended. The patient was provided with a validated, fully automated home S-BPM device (A and D UA-767PBT, A and D Company, Japan) and was instructed to perform 2 home BP measurements, separated by 5 minutes of rest and in the seated position, at least two times per day, morning and evening. Home BP readings were recorded by the patient in a log book and in CARDIOcheckAPP (medical app for iOS and Android platforms, by Medical Mate srl, Italy) in order to share, by smartphone, self-tested BPMs with her cardiologist (data summarized in Figure). As in the previous year, her BP was well controlled in case of hot temperature, with the need to reduce the therapy in the summer or in the case of stay in hot countries for some hypotensive episodes, but it rose again in the winter until she had a new hypertensive crisis in February 2014. Indeed, on this occasion, she came back to our ER with an occipital and supraorbital headache (BP: 200/120 mmHg), and she was re-hospitalized. During the hospitalization, she performed other screening exams for organ damages and for more uncommon causes of secondary hypertension, (immunologic diseases such as vasculitis, systemic sclerosis, systemic lupus erythematosus, Sjogren's syndrome, polyarthritis nodosa, antiphospholipid syndrome), by serology and nailfold capillaroscopic, both negatives for autoimmune rheumatic diseases. In addition, an evaluation with the Endo-PAT 2000 system was performed, with a resultant pattern of augmented arterial stiffness (5). Furthermore, 24-hour BP monitoring showed lack of control of her BP despite the maximum tolerated medical therapy.

After multidisciplinary discussion, also including specialists beyond the area of cardiovascular medicine (neurologists and nephrologists), it was agreed new indication for RDN, performed this time with an ultrasound denervation system, the ReCor Paradise (ReCor Medical, Ronkonkoma, NY, USA). Like the first time, the procedure was acutely very effective (invasive arterial BP measurement on therapy during the procedure: 220/110 mmHg; H-BPM at discharge: 90/60 mmHg). Regrettably, this time the procedure was complicated by a prolonged hypotension (BPM 75/35) which caused a loss of consciousness and a reduction of the visual acuity of the left eye associated with hyposthenia of the left lower limb. In this contest, a head MRI was performed, and multifocal, hyperintense at a long-TR sequence, parenchymal alterations involving the supratentorial bilateral white matter were seen. These lesions were interpreted as of "specific significance" by radiologist, and a diagnosis of functional stroke was performed (6).

After the neurological rehabilitation, she was discharged without antihypertensive therapy. Unfortunately, again, her BP values were adequate for summer months, but during the winter they increased again, with the need of increase the antihypertensive drugs number and posology.

Even though two RDN procedures were not totally effective, our patient has now an easier control of her BP values, despite frequent peaks also after the second procedure, as in the previous two years.

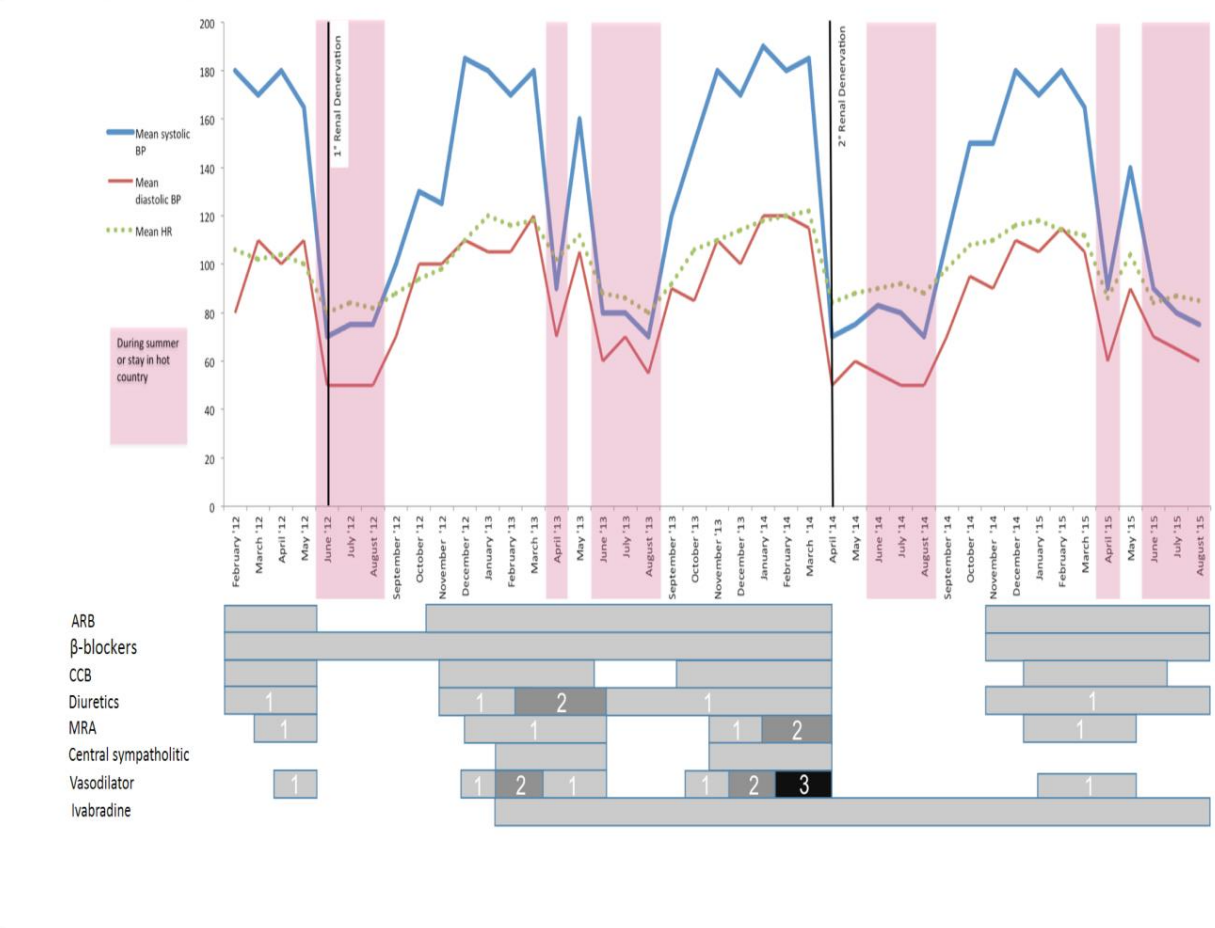

Figure 1. Home measurement of blood pressure (BP) and heart rate (HR) from February 2012 through August 2015 provided with a validated, fully automated home self-tested BP measurement (A and D UA-767PBT device, A and D Company, Japan), and recorded by the patient in CARDIOcheckAPP (medical app for iOS and Android platforms, by Medical Mate srl, Italy) in order to share, by smartphone, self-tested BP measurements with her cardiologist. Note the lack of efficacy for two renal denervation procedures. β-blockers were either nebivolol or propranolol; calcium antagonist: amlodipine or diltiazem; AT1 antagonist: telmisartan or irbesartan; diuretic: hydrochlorothiazide and/or furosemide; aldosterone antagonist: spironolactone; canrenone and/or amiloride; central sympatholytic: clonidine; vasodilators: doxazosin, nitroglicerin, and minoxidil; ivabradine.

Table 1. Instrumental and laboratory examination performed after the first hypertensive crisis. BP: blood pressure; O-BPM: office-blood pressure measurement; H-BPM: hospital-blood pressure measurement; CT: computed tomography; MRI: magnetic resonance imaging; SAB: supra-aortic branches; TT: trans-thoracic; IA-BPM: invasive arterial blood pressure monitoring; S-: serum; U-: urinary; DU-: daily urinary; TSH: thyroid stimulating hormone; Aldo: aldosterone; Adr: adrenalin; Nor: noradrenaline; ACE: angiotensin converting enzyme.

TIME	Instrumental examination	Comments	Laboratory test
January 2012	O-BPM.	180/100 mmHg	Not performed
	Renal arteries echo-Doppler; Abdomen echography, thin-slice CT, and MRI; encephalic MRI.	All normal	Urinalysis: no proteinuria, electrolytes alterations or presence of cocaine and amphetamine metabolites.
	Echocardiogram; Kidney echo-Doppler; Fundus oculi; SAB echo-doppler.	All normal	S-Creatinin 0.82*; S-Urea 33*; S-Na^+ 140#; S-K^+ 4.71#; S-Ca^{++} 2.44#;
March 2012	O-BPM	220/100 mmHg	S-Aldo 140.8 pg/mL;
	24/hrs H-BPM	180/100 mmHg	U-Adr 2.6§; DU-Adr 4.7 µg/24h, U-Nor 16.5§; DU-Nor 29,7 µg/24h.
June 2012	IA-BPM	160/100 mmHg	Not performed
	24/hrs H-BPM (after 1st RDN)	100/60 mmHg	
February 2013	Head MRI	Normal	S-Creatinine 0.85; S-Na^+ 141; S-K^+ 4.21; S-Ca^{2+} 2.35. TSH; fT3; fT4; U-Nor 17§; U-Adr 2.5§; S-Aldo 139 pg/mL.
	Abdomen MRI gadolinium; TT-Echocardiogram.	Normal	
	O-BPM	210/130 mmHg	
	24/hrs H-BPM	210/120 mmHg	
February 2014	Capillaroscopy	NEG for vasculitis and immunologic diseases	S-ACE 48 U/L (37-137); S-Aldo orthostatic 287 pg/mL (70-350); S-Renin orthostatic 2.2 pg/mL/h (1.5-5.7).
	Coronarography	Normal	
	24/hrs H-BPM	220/120 mmHg	
	IA-BPM	220/110 mmHg	
	24/hrs H-BPM (after 2nd RDN)	90/60 mmHg	

*: measured in mg/dL
#: measured in mmol/L
§: measured in µg/L

Discussion

We do not already know which could be the underlying cause of hypertension in this patient. We did not specifically look for some extremely rare causes of secondary hypertension, such as Liddle's syndrome, type E brachydactyly, and neurovascular contact, but all imaging and laboratory exams performed and also clinical examination could reasonably lead us to rule out this sporadic conditions (5,6). Despite the relevant BP fluctuations (very low BP in the summer or in case of stay in hot countries) and the recurrence of sinus tachycardia, the absence of primary symptoms of dysautonomia (e.g. excessive fatigue, thirst, sweating and mydriasis, constipation, etc…) made us also to exclude the most common causes of autonomic dysfunction (9).

She was refractory not only to the maximum tolerated medical antihypertensive therapy but in the long term-also to a device-related antihypertensive treatment, such as the RDN. It is known from the literature that the RDN can improve BP control in hypertensive patients, but this effect is lost if reinnervation occurs, as it in many cases does (10). It is important to underline that our patient underwent RDN before the publication of the SIMPLICITY HTN-3 trial (9,10).

For us, this case revealed itself very hard to manage: extremely deep BP oscillations and post-procedural complications led us to doubt about patient's compliance. These were the main reasons that deceived us to perform other device-related treatment, such as baroreflex stimulation or even deep-brain stimulation of the ventrolateral periaqueductal gray/periventricular gray (11,12). Furthermore, we were also astonished by the absence of organ damages after many years of uncontrolled hypertension. Nevertheless, the psychiatric consultancy, the 24-hour BP monitoring and, above all, witnessed ingestion of drug therapy allowed us to rule out Münchausen's syndrome or another form of patient nonadherence or substances abuse favoring hypertension, leaving us without a true explanation

about the cause of this refractory hypertension.

References

1. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, White A, 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:e510-26.
2. White WB, Turner JR, Sica DA, Bisognano JD, Calhoun DA, Townsend RR, et al. Detection, evaluation, and treatment of severe and resistant hypertension: proceedings from an American Society of Hypertension Interactive forum held in Bethesda, MD, U.S.A., October 10th 2013 J Am Soc Hypertens 2014;8:743-57.
3. Egan BM, Zhao Y, Axon RN, Brzezinski WA, Ferdinand KC. Uncontrolled and Apparent Treatment Resistant Hypertension in the United States, 1988 to 2008. Circulation 2011;124:1046-58.
4. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, et al. Recommendations for blood pressure measurement in humans and experimental animals: Part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Circulation 2005;111:697-716.
5. Moerland M, Kales AJ, Schrier L, van Dongen MGJ, Bradnock D, Burggraaf J. Evaluation of the EndoPAT as a Tool to Assess Endothelial Function. Int J Vasc Med 2012;2012:904141.
6. Stone J, Warlow C, Sharpe M. The symptom of functional weakness: a controlled study of 107 patients. Brain 2010;133:1537-51.
7. Jordan J, Toka HR, Heusser K, Toka O, Shannon JR, Tank J, et al. Severely impaired baroreflex-buffering in patients with monogenic hypertension and neurovascular contact. Circulation 2000;102:2611-8.
8. Pepersack T, Allegre S, Jeunemaître X, Leeman M, Praet JP. Liddle syndrome phenotype in an octogenarian. J Clin Hypertens (Greenwich) 2015;17:59-60.
9. Martínez-Martínez LA, Mora T, Vargas A, Fuentes-Iniestra M, Martínez-Lavín M. Sympathetic nervous system dysfunction in fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and interstitial cystitis: a review of case-control studies. J Clin Rheumatol 2014;20:146-50.
10. Esler M. Renal denervation for hypertension: observations and predictions of a founder. Eur Heart J 2014;35:1178-85.
11. Sciurba F, Rennard SI. Rationale for a redundant formulary. The Hawthorne effect and the art of medicine. Am J Respir Crit Care Med 2015;191:1224-5.
12. 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;370:1393-401.
13. Briasoulis A, Bakris G. Efficacy of baroreflex activation therapy for the treatment of resistant hypertension. EuroIntervention 2013;9:R136-9.
14. Patel NK, Javed S, Khan S, Papouchado M, Malizia AL, Pickering AE, et al. Deep brain stimulation relieves refractory hypertension. Neurology 2011;76:405-7.