CASE REPORT

A 36 Year Old Woman with "Difficult-to-Treat" Hypertension: Endocrine or Resistant Hypertension?

Alaaeldin M. Bashier, Fatheya F. Al Awadi, Puja Murli Thadani, Azza Abdulaziz Khalifa

Division of Endocrinology, Department of Medicine, Dubai Hospital, Dubai, United Arab Emirates.

Corresponding author: Dr. Alaaeldin M. Bashier E-mail: aekhidir@dha.gov.ae
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Abstract

A thirty six year old Emirati female who had had hypertension for 5 years is presented. Her blood pressure has been consistently above 160/110 mmHg, despite being treated with more than 5 antihypertensive drugs. Work up for secondary hypertension was repeatedly negative locally and at two world-renowned endocrine units in London. Ultimately, she underwent "catheter guided renal sympathectomy", which resulted in good blood pressure control readily achievable on single antihypertensive agent. The diagnostic and management challenges of the case are presented and the efficacy of the therapeutic procedure in treating resistant hypertension is discussed. We also appraise the evidence-base for potential place of this procedure in the current guidelines for management of hypertension.

Keywords: Resistant hypertension, Catheter based renal sympathectomy, Secondary hypertension.

List of appreviations:

FBC: full blood count, PAC/PRA: Plasma aldosterone concentration/plasma renin activity, ECG: Electrocardiogram, LVH: Left ventricular hypertrophy, USS KUB: Ultra sound kidney, ureter and bladder, CT: Computed tomography scan, CXR: Chest X-ray, ACE: Angiotensin converting enzyme, VMA: Vinyl mandellic acid, RAAS: Renin-Angiotensin-Aldosterone System, ECHO: Echocardiography

Case History

A 36 years old Emirati female with history of hypertension for 2 years was seen in endocrine clinic for evaluation for the possibility of secondary endocrine hypertension. This was considered on the basis of having had symptoms of palpitations, headache, easy fatigue and sweating. At that time, she was receiving Lisinopril, Amlodipine and Indapamide. There was no family history of hypertension. Her blood pressure in clinic was 145/90mmHg. With view to evaluate her for secondary hypertension, she was advised

to stop Indapamide and to increase the dose of Amlodipine to 10mg daily. However, she was lost to follow up. She turned up in cardiology clinic three years later, with difficult breathing and uncontrolled hypertension. She was admitted to the ward for blood pressure control and to evaluate her for evidence of left ventricular hypertrophy. During this admission, she had several very high blood pressure readings despite being on Amlodipine 10mg, Carvedilol 25mg bid, Hydrochlorothiazide 25mg, Spironolactone 600mg, and Perindopril 10mg daily. The initial biochemical, cardiac and imaging studies are summarized in Tables 1 and 2. Rest of other relevant investigations are given in table 1.

Given the findings on CT scan, she was referred to endocrine team for further evaluation for adrenal cause. Examination revealed a calm and comfortable patient. Her BP was 180/112mmHg, pulse was 97 beats per min, body mass index (BMI) was 25.6 kg/m2. There was no radio-femoral delay. No striae, no supra clavicular fat pads, and no buffalo hump were noted. Retinal examination revealed grade 2 hypertensive retinopathy. Systemic examination only showed 2 cm peri-umblical scar of previous liposuction. The initial clinical impression was that she has secondary hyperaldosteronism, and we thought that we needed to repeat all her investigations off diuretics, ACE inhibitors and spironolactone. During her stay in the endocrine ward, her systolic blood pressure did not drop below 180-220 mmHg systolic, and 100-140mmHg diastolic. This made

Table 1. Results of Initial Basic Haematological and Biochemical Investigations.

Measurements.	**Patient's Data**	**Comments**
FBC, ESR, and LFT	Normal	-
Serum Creatinine	0.8mg/dl	-
Urea	23mg/dl	-
Serum K	3.8mg/dl	-
Serum Na	141mg/dl.	-
24hrs urine cortisol	26ug/24hrs	NR (6.2-29)
Serum Renin	4.2ng/ml/hr.	NR (0.5-2.6)
Serum Aldosterone	975nmol/l	NR (28-444)
PAC/PRA	= 8.35	-

Table 2. Summary of Cardiac and Imaging Studies.

Investigations	**Results and implications**
Electrocardiogram	Evidence of left ventricular hypertrophy.
Chest X-ray (Figure 1)	No cardiomegaly, no features to suggest Coarctation of aorta.
Echocardiography	Left ventricular ejection fraction of 55%, grade 1 diastolic dysfunction; there were no valvular or septal defects.
Ultrasound scanning for kidney ureters and bladder (KUB)	Normal
Renal angiogram	No evidence of renal artery stenosis, fibromuscular dysplasia, or beading of renal artery
Computed tomography for adrenal glands (Figure 2 &3)	The left gland shows widening of the limbs associated with apparent nodularity with minute iso-dense nodules of questionable significance.

Table 3. Results of Investigations for endocrine causes of hypertension.

Measure	**Patient's Results**	**Reference Ranges and Comments.**
Urinary VMA*	10.9 umol/24hrs	<33
Serum 11 Deoxycorticosterone	28ng/dl (85pmol/l)	40-170ng/l (121-518pmol/l))
Serum 11 deoxycortisol	0.3ug/l	(NR 0.2-1.1),
Serum 17OH Progesterone	4.7nmol/l	<10 nmol/l
Serum and urinary fractionated metanephrines**	Negative	Negative

* VMA Vinlymanedilic acid; ** Taken on multiple occasions.

Table 4. Etiology of Resistant Hypertension

Pseudo-resistant Hypertension	Errors in blood pressure measurement
White-coat hypertension	Poor adherence to medications
Primary hyperaldosteronism	
Atherosclerotic vascular disease	
Sleep apnoea	
Chronic kidney disease	
Phaeochromocytoma	
Aortic coarctation	
Cushing's disease	
Hyperparathyroidism	

Table 5. Learning Points

1. Resistant hypertension is defined as elevated systolic blood pressure ≥160mmHg despite treatment with at least 3 anti-hypertensive medications from different drug classes, including a diuretic.
2. Negative serum and urinary fractionated metanephrines in a symptomatic patient excludes the diagnosis of phaeochromocytoma.
3. When managing resistant hypertension consider adding drugs that act at different pathogenic mechanisms of hypertension to achieve good blood pressure control.
4. Catheter based renal sympathectomy is a new procedure that has proved effective in managing patients with resistant hypertension.

it quite difficult to stop all antihypertensive medications, except for spironolactone, She remained on the ward for 2 months, her blood tests and urine collection were repeated (Table 3). She continued to have symptoms and one day she complained of palpitations and abdominal pain and collapsed in her room. She got admitted to Intensive Care Unit (ICU), where she has been started on labetalol infusion, this managed to control her blood pressure to 135/90mmHg most of the time. After discharge from ICU her blood pressure remained high at >180/110mmHg despite being on oral Labetalol 400mg, Amlodipine 10mg daily, Spironolactone 200mg daily, Indapamide 1.5mg daily, Perindopril 10mg daily and Terazosin 5mg at bed time.

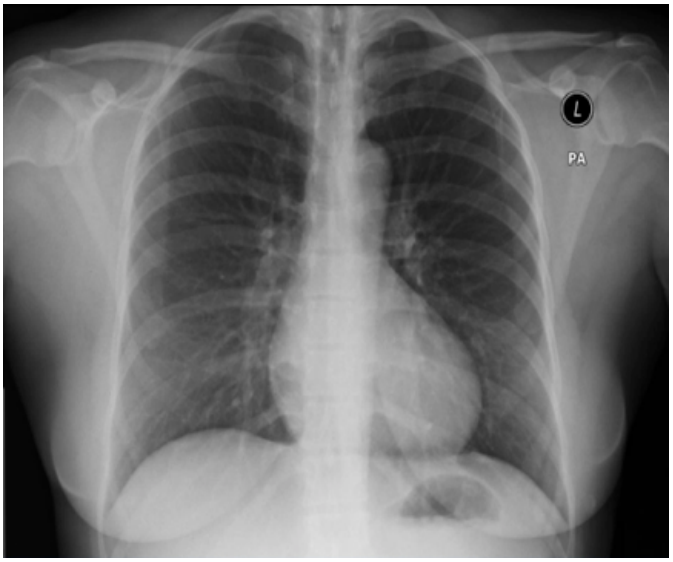

Figure 1. No cardiomegaly, no features to suggest Coarctation of aorta.

After leaving the hospital, she was followed up in clinic; we tried (pharmacologically) to totally block the RAAS system, as well as the sympathetic system. Her regimen included Terazosin, Aliskerin 300mg, Valsartan 160mg, Carvedilol 25mg bid, Amlodipine 10mg od, Moxonidine 0.4mg, Methyl Dopa 500mg bid, Spironolactone up to 600mg, and hydrochlorothiazide, with no good response. Blood pressure remained high. Her management posed several practical and ethical issues. These included decisions regarding the need for admission to hospital and length of stay. Sick leave was another difficult issue as she is too young to retire, and could not have sick leave for many months. On the other hand it not safe to resume her duties with uncontrolled hypertension.

We sought a second opinion from 2 experienced endocrinologists in London, United Kingdom. Who advised adding clonidine to her regimen after the hypotensive response during clonidine suppression test, other wise there was no change to her regimen. In her follow up visits in the clinic we noticed that she is more depressed and psychologically unstable, she agreed that all these symptoms

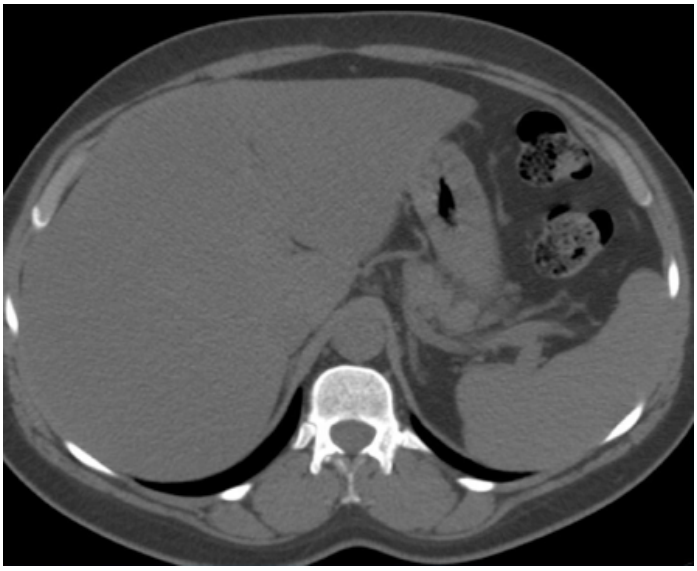

Figure 2

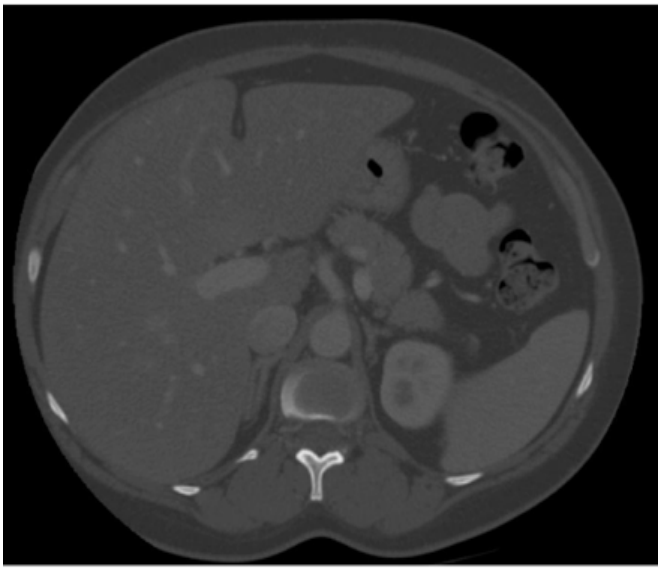

Figure 3

The left gland shows widening of the limbs associated with apparent nodularity with minute iso-dense nodules of questionable significance.

were related to clonidine, which had to be withdrawn. We were suspicious initially of phaeochromocytoma (given her symptoms, elevated blood pressure readings and the adrenal imaging reports). The negative results of fractionated metanephrines almost excluded the diagnosis, and we believed that we are dealing with a resistant hypertension. We advised her to visit a specialised centre in US for a third opinion. There she was offered catheter based renal sympathectomy, which she accepted. In her follow up visits to the clinic we have seen a remarkable improvement in blood pressure with the latest 138/88mmHg on metoprolol 50mg bid 1 year after the procedure.

Discussion

The clinical scenario described exemplified by the present case illustrates the failure of pharmacological therapy in management of patients with "resistant or difficult-to-treat hypertension". Resistant hypertension is defined as elevated systolic blood pressure ≥160mmHg despite treatment with at least 3 anti-hypertensive medications from different drug classes, including a diuretic. It is essential to include a diuretic due to persistent volume expansion, which has been demonstrated by elevated levels of brain-type natriuretic peptide and atrial natriuretic peptide (1). Since resistant hypertension affects only a minority of treated hypertensive patients, it was mandatory that we attempted to exclude secondary causes of hypertension prior to labelling such patient as 'resistant', 'refractory' or 'difficult-to-treat' hypertension (Table 4). In such cases of pharmacological failure, invasive device-based treatment approaches have emerged as an attractive therapeutic option that can be used in addition to anti-hypertensive medications for lowering blood pressure in multi-drug resistant hypertension. A new catheter based system, the simplicity catheter, has been developed for bilateral selective and sequential sympathetic denervation of the kidneys through an endovascular approach. It involves focal delivery of 4-6 low-power radiofrequency energy ablations (5-8W) along the length of both renal arteries. Prior to performing this procedure it is essential to screen patients for suitable renal vasculature and provide appropriate systemic anti-coagulation. Data available for the effectiveness and safety of this novel technique is discussed subsequently.

In a proof-of-principle study including 50 patients with resistant hypertension, a significant reduction of 14/10mmHg in blood pressure at one month among patients who underwent catheter-based renal sympathetic denervation. This effect continued to persist until the end of the study where a reduction of 27/17mmHg was noted at 12 months. Six patients did not experience a significant (≤10mmHg) drop in SBP and were considered non-responders. On the other hand, five patients who were deemed unsuitable for intervention due to their renal vascular anatomy experienced no change in their blood pressure during this period (2). A further extension of this cohort in the Simplicity-HTN1 study revealed a consistent blood pressure lowering effect with a drop in systolic and diastolic blood pressures up to 24 months thus establishing the safety and efficacy of this procedure (3). In both phases, success rates were 96 and 97%. The major limitation in these studies was that they did not include any control groups with which comparisons could be made with respect to blood pressure lowering effect and eGFR.

Simplicity HTN-2 study randomized 106 patients to receive standard therapy and renal denervation or standard therapy alone. It is noteworthy that this study included a two-week wash-in period to ensure a stable, but unremitting hypertension in included patients. Fifty-two patients underwent renal denervation (with 3 lost to follow-up) with a mean reduction of 32/12mmHg in blood pressure at 6 months compared to no significant change in the standard therapy group. Approximately, 84% patients had a reduction of at least 10mmHg in systolic blood pressure at 6 months, and in this study, the procedures were carried out without any serious device-related or procedure-related adverse events (4). Moreover, in patients with hypertension and mild renal disease (eGFR between 45-60ml/min), the procedure did not worsen renal function (as measured by eGFR at 6 months), suggesting that this procedure is safe even in those with mild renal disease. There was no significant difference noted in the decline of eGFR between the groups. Results from a recent study including 15 patients with resistant hypertension and stage 3-4 chronic kidney disease demonstrated a blood pressure reduction of 33/19mmHg at 12 months, thus suggesting that renal sympathetic denervation is safe in this cohort of patients in the short-term (5). Therefore, Simplicity HTN-2 study confirmed the findings of the study established the efficacy of catheter based renal denervation for the treatment of resistant hypertension.

Radiofrequency ablation is associated with a theoretical long-term risk of fibrotic scarring that may result in the development of focal renal artery stenosis or aneurysm. For this purpose, imaging of the renal arteries 6 months after intervention was carried out in 81 out of 153 patients in the

Simplicity HTN-1 study and 43 out of 52 patients in the Simplicity HTN-2 study (3,4). Data from both these studies showed an absence of renal artery lesions, effectively establishing that this procedure is not associated with the risk of renal artery stenosis due to stricture formation and it does not have any adverse effect on renal function. The progression of underlying atherosclerotic stenosis was observed in one patient after denervation, in the Simplicity HTN-2 study, but this did not require treatment.

Recent studies have also shown that the effect of renal denervation extends beyond reduction of blood pressure. In a small study, Mahfoud et al. showed that renal denervation improved glucose metabolism (by reducing fasting blood glucose levels) and insulin sensitivity (by decreasing insulin and C-peptide levels) in addition to significantly lowering blood pressure (6). Another non-randomized, open-label study demonstrated an improvement in the severity of sleep apnoea in patients treated with renal denervation, as well as improvement in blood pressure and blood glucose control (7).

Final Remarks

The current case presents several learning points (Table 3). Catheter based selective renal sympathectomy is a novel treatment modality shown to be safe and effective in the treatment of resistant hypertension with no device related complications reported so far. Although the Simplicity HTN-2 trial remains the largest randomized, controlled study assessing the efficacy of the bilateral renal denervation thus far, several questions regarding the long-term safety of this procedure and its absolute benefits on cardiovascular mortality remain unanswered. However, current evidence for this interventional procedure provides sufficient promising data to justify continuing research on this methodology. Further investigation into the effects of this procedure will also allow a better understanding of the underlying pathophysiology, thereby enabling identification of which type of patients will particularly benefit from this procedure. In view of the growing evidence base, renal denervation might have the potential to revolutionize the treatment of hypertension and may be incorporated into international treatment guidelines in the future.

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