Truly Refractory Hypertension

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What really is refractory or resistant hypertension? Twenty years ago, Setaro and Black defined the condition as blood pressure >140/90 mm Hg, no evidence of secondary hypertension, maximal doses of at least 2 appropriate antihypertensive agents, and sufficient treatment duration to allow the treatments to be effective. Today, we would probably expand the definition to at least 3 agents or patients who do not respond to 3 agents, including a thiazide diuretic plus mineralocorticoid-receptor inhibition. Thirty years ago, Swales et al performed a trial of regimens for such patients. One of the following 4 regimens was used: oral diazoxide, minoxidil, captopril, or quadruple therapy (diuretic+β-adrenoceptor blocker+hydralazine+prazosin). Despite the severity of hypertension, blood pressure could be controlled in almost all these patients. Since then, sleep apnea has come under scrutiny as a common unappreciated cause. Ruttanaumpawan et al found that about half of their 42 therapy-resistant patients with hypertension were suffering from obstructive sleep apnea. Of course, there is always the lingering possibility that the patients are just not ingesting their medicines, and novel strategies have been developed to deal with that issue. The advent of device-related treatments has pretty well laid the issue of refractory hypertension to rest. Typing the condition into search engines invariably leads the searcher to articles on catheter-based renal denervation. We present a case that we believe is an example for truly resistant hypertension, and we like to coin the term device-resistant hypertension into the debate about uncontrollable hypertension.

The Case

Our patient, who kindly provided written consent for this report, is a slender (body mass index, 17.4 kg/m²) 51-year-old woman, who was normotensive until age 36 years. By that time, she had had 4 uneventful pregnancies without complications. Her mother was hypertensive, and her father also had elevated blood pressure and a myocardial infarction at age 70 years. All her children are normotensive. At age 37 years, her blood pressure proceeded to increase, and antihypertensive treatment was initiated. By the time she was 43 years old, she was receiving up to 7 antihypertensive drugs and had mean 24-hour ambulatory values of 220/120 mm Hg recorded without nocturnal dipping. The patient had also developed 5 fainting episodes that could not be attributed to a cardiovascular cause. An electroencephalogram suggested the presence of focal epilepsy, and a neurologist initiated treatment with lamotrigine, after which no further episodes occurred, and the electroencephalogram normalized.

The patient was referred to numerous hypertension specialists and was extensively evaluated with negative screens for pheochromocytoma. Her renin and aldosterone values were in the normal range, thin-slice computerized tomography of the adrenal glands excluded adenoma or hypertrophy, renal Duplex-Doppler studies and MRI of the renal vessels were normal, and MRI of the cerebral vessels showed no evidence for neurovascular contact syndromes involving the posterior-inferior cerebellar artery. Tests for autoantibodies directed at the type 1 angiotensin II receptor were repeatedly negative. The patient did not have obstructive sleep apnea. Twenty-four-hour urine collections for sodium, potassium, catecholamine metabolites, and drug metabolites (cocaine or amphetamines) were unremarkable on multiple occasions. The patient was counseled about prudent nonpharmacological lifestyles. Because serum electrolytes were invariably normal, no genetic testing was performed for Mendelian syndromes. Urine analyses for antihypertensive drug metabolites strongly suggested that the patient was compliant. The patient was referred to the Experimental and Clinical Research Center in Berlin-Buch.

We encountered a slender pleasant but concerned woman. On physical examination, the heart rate was normal, the blood pressure was 280/130 mm Hg, while ingesting torasemide, clonidine, amlodipine, bisoprolol, candesartan, minoxidil, and urapidil. We assayed the first 5 agents and found them to be present; we had no assays for minoxidil or urapidil available, but nonetheless felt that poor compliance was unlikely. Funduscopic examination revealed increased arterial light reflex and narrowing, but no hemorrhages, exudates, or papilledema. The chest was clear, the heart was surprisingly little enlarged. There were no abdominal bruits. The blood
pressure values in the lower extremities resembled those in the upper extremities. There was no peripheral edema. A urinalysis was normal with no proteinuria. An echocardiogram showed only modest left ventricular hypertrophy, a 24-hour urine specimen revealed a sodium excretion of 167 mmol/24 hour. Arterial blood gases, electrolytes, renin, and aldosterone levels were normal, as were metanephrines and normetanephrines.

The patient was followed in Berlin-Buch for 2 years and afterward at Hannover Medical School (Figure 1). Nine medications were tried, generally in combinations of 5 to 7 preparations. Oscillometric clinic blood pressures were rarely <200/120 mm Hg. Some heroic and, admittedly, peculiar treatments were attempted, including a plasma exchange that was not helpful.9 Within a clinical trial (Rheos Pivotal Trial, ClinicalTrials.gov NCT00442286), a baroreflex stimulator (Rheos, CVRx, MN, USA) was implanted.10,11 Initially, an encouraging acute effect was observed with a decrease in blood pressure of 60 to 80 mm Hg. However, chronic stimulation was disappointing, and her blood pressure continued to increase to values up to 280/150 mm Hg. Later on, the initial baroreflex stimulator had to be explanted because of local complications and was replaced by a newer model (Barostim Neo, CVRx, MN).

On one occasion, we brought the patient to the clinical research center and placed a catheter into her right radial artery (Figure 2). Under direct vision, she ingested bisoprolol, candesartan, clonidine, minoxidil, urapidil, torasemide, and spironolactone. The blood pressure measurements were continued for several hours. Her blood pressure gradually decreased, but only from 280/150 mm Hg to 250/130 mm Hg.

On another occasion, we measured muscle sympathetic nerve activity (MSNA), while continuously noninvasively monitoring blood pressure with a Finapres device (Ohmeda, USA) checked by brachial oscillometric (Dinamap, Critikon, USA) measurements in the opposite arm (Figure 3).12 Blood pressure values of 200/130 mm Hg were observed and, nevertheless, the MSNA activity was normal albeit for someone with a normal blood pressure. We next administered sodium nitroprusside and lowered blood pressure acutely by =20 mm Hg. MSNA promptly increased. On yet another occasion, intravenous urapidil hardly decreased blood pressure but led to a considerable increase in sympathetic outflow. Adding clonidine, a centrally acting sympatholytic,13,14 led to modest reductions in blood pressure, although MSNA clearly remained elevated (Figure 4).

The patient was subsequently followed at the Hannover Medical School. Here, a renal nerve ablation was performed in the recommended fashion. Eight radiofrequency applications were performed along both renal arteries (Symplicity Catheter System, Ardian, CA).15 The patient denied permission for additional MSNA studies. However, we were able to measure blood pressure at all 4 extremities and cardiac output (foreign gas rebreathing) immediately before the procedure. These

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**Figure 1.** Office measurements of blood pressure (BP) and heart rate (Dinamap, Critikon, USA or BP Tru, Smiths Medical PM, Inc, UK) from February 2007 through August 2012. Throughout the entire period, the patient was on antihypertensive combination therapy. Note the lack of efficacy for plasma exchange, long-term baroreflex stimulation (Rheos, CVRx, MN), and renal denervation (Symplicity, Ardian, CA). β-blockers were either nebivolol, bisoprolol, propranolol, or metoprolol; calcium antagonist: amlodipine or manidipine; ACE inhibitor: delapril or ramipril; AT1 antagonist: telmisartan or candesartan; renin inhibitor: aliskiren; diuretic: torasemide, aldosterone antagonist: spironolactone; central sympatholytic: clonidine; vasodilators: urapidil, doxazosin, molsidomin, dihydralazine, and minoxidil.
studies document the severe and persistent hypertension (left arm: 299/182 mm Hg; right arm: 277/179 mm Hg; left leg: 306/179 mm Hg; and right leg: 304/177 mm Hg). Cardiac output was 5.3 l·min⁻¹, and systemic vascular resistance was more than doubled (>3000 dyn·s·cm⁻⁵) compared with normal values. Several months after this procedure, the patient was still receiving an 8-drug regimen with systolic blood pressures between 250 and 300 mm Hg. Although 2 device-related therapies that putatively function by reducing sympathetic tone¹²,¹⁷ did not help our patient, we still have reason to believe that abnormal autonomic function is contributing to her problem.¹⁸ Through the Internet, our patient became aware of a third novel device-related therapy to address sympathetic tone. She traveled to Bristol, UK, and was evaluated for a deep-brain stimulator to lower her blood pressure.¹⁹ The Bristol group was initially very hesitant about implanting such a device into our patient, although we understand that the investigators are reconsidering that decision.

Comment

We do not know what is wrong with our patient and why she is refractory not only to conventional medications but also to device-based antihypertensive treatments. We would speculate that something is wrong with her neuroregulatory circuits. She still has normal MSNA despite very high blood pressures. In that way, she resembles a family with genetic hypertension and type E brachydactyly that we are investigating.²⁰ Those patients also have neurovascular contact, which the current patient does not. In the patients with brachydactyly, basal blood pressure was increased even during sympathetic and parasympathetic nerve traffic interruption. However, sympathetic stimuli caused an excessive increase in blood pressure. This excessive response could be explained by increased sympathetic nerve traffic or increased vascular sensitivity. We had suggested that baroreflex buffering is severely impaired in those patients. We could not test our patient with refractory hypertension with autonomic blockade. Interestingly, the patients with brachydactyly do not have refractory hypertension, although...
they commonly require 3 drug classes for control. Centrally acting agents were no more effective than other drugs. In contrast, clonidine and urapidil seemed strangely ineffective in our patient.

Two device-related treatments that ostensibly decrease sympathetic tone did not help our patient. We were interested to learn that a third device-related treatment is being developed. Patel et al described a 55-year-old man who had developed a stroke. In the peristroke period, refractory hypertension developed. Deep-brain stimulation of the ventrolateral periaqueductal gray/periventricular gray was performed, as a treatment for a refractory pain syndrome. Serendipitously, immediately after deep-brain stimulation, blood pressure gradually decreased (trough of 80/53 mm Hg) prompting withdrawal of antihypertensive medications. The authors suggested that periaqueductal gray/periventricular gray stimulation can produce a large, sustained lowering of blood pressure in a patient with refractory hypertension, which seems to be efficacious because all antihypertensive medication could be withdrawn.

Nonresponders to device-based antihypertensive therapies have been reported for renal denervation and for baroreflex stimulation. The true magnitude of the problem is difficult to ascertain, given the limited number of patients enrolled in properly controlled clinical trials. Hoppe et al reported on patients with uncontrolled blood pressure after renal denervation, who were then entered in a baroreflex stimulation trial. All 6 patients responded to baroreflex stimulation, with a mean reduction in blood pressure and heart rate that was similar to those in patients who had not undergone renal denervation. Yet, our observations suggest that a subset of patients with device-resistant hypertension does not respond to either intervention. Nonresponders to device-based treatments for hypertension are arbitrarily defined in clinical trials, typically as a decrease in blood pressure <10 mm Hg or <20 mm Hg. Obviously, this definition does not insist on normal blood pressure values. In our view, a more comprehensive definition of device-resistant hypertension should be sought to facilitate further research.

For us, this patient was a humbling experience indeed. We also came to admire her patience and fortitude. She was willing to put up with a great deal of additional testing, some of which was quite invasive. We are hardly in a position to advise her further. We were struck by how well she tolerates these carefully documented pressures in terms of relatively little target-organ damage. Her fundi are hardly indicative of severe hypertension, and her heart is not particularly enlarged. She still has no proteinuria, and her glomerular filtration rate remains normal. In this regard, she also resembles our patients with brachydactyly. Never again will we be smug about colleagues who comment that their patients have uncontrollable blood pressure values.

None.

References

Figure 4. Intravenous urapidil was partly counterregulated by increases in heart rate and sympathetic vasoconstrictor activity (muscle sympathetic nerve activity [MSNA]). On-top infusion of clonidine decreased sympathetic vasoconstrictor tone and blood pressure to some extent.


