

If I Had Resistant Hypertension Eoin O'Brien

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If I Had Resistant Hypertension

Eoin O'Brien

This essay is influenced by the circumstances in which I find myself. That I am a certain age, that I live in a small island with a health service struggling to provide adequate health-care to 4.5 million people within the financial constraints of a massive recession, and that the diagnosis and treatment of hypertension in Ireland follows mainly European trends have all shaped the content of what is a personal experience, as the title of this series suggests it should be. It must be accepted, therefore, that the circumstances for diagnosing and managing resistant hypertension in Ireland may differ somewhat from those that pertain in, for example, New York, but I suspect, however, that the principles of management are similar being based on the recommendations of international guidelines.

Circumstances of Diagnosis

Let us say that I am over 60, that my mother had hypertension but lived into her 70s when she died of cancer, and that there is no paternal history of cardiovascular disease. I have no previous history of illness. My lifestyle is, at least by my assessment, healthy in that I do not smoke, enjoy my wine in what might be regarded as slightly above the weekly norm, maintain normal weight, eat sensibly without adding salt to my food, and I exercise daily by swimming in the sea, across from my home, in all weathers. My only medication is atorvastatin 20 mg daily taken more for its vascular protective potential (arising from my belief in the results of the ASCOT [Anglo-Scandinavian Cardiac Outcomes Trial] study in which I was an investigator) than its lipid-lowering properties because my lipids have always been normal. Because of an interest in hypertension, I occasionally, very occasionally, check my own blood pressure (BP).

I am surprised 1 day to read on my oscillometric display a figure of 154/94 mmHg and when repeated with a different device some days later the reading was 156/95 mmHg. I take myself off to a trusted general practitioner (GP), who has cared for my family for many years, who confirmed my hypertensive status (160/100 mmHg); I note the terminal digit rounding with interest but accept that I am likely to be hypertensive. He sends me for urinalysis, biochemistry, liver function tests, fasting lipids and glucose, an ECG, echocardiography, and abdominal ultrasound, all of which are normal. On my next visit, he reaches for his prescription pad, but I gently restrain him, suggesting that I should have a 24-hour ambulatory BP measurement (ABPM).

Ambulatory BP Measurement

I am referred to a private clinic where, after waiting some 40 minutes, a technician applies a cuff to which the monitor on my waist is attached, and after a brief explanation as to how it works, she sends me on my way. I return the next day and after a wait of some 30 minutes, she removes the monitor and instructs me to return to my GP, but not for a week, to permit her time to mail the results to him. I do as instructed, and after waiting some 20 minutes (there is purpose in totting the waiting time), my friendly GP shows me the result. I have anticipated 2 possible outcomes: either the ABPM will demonstrate white coat hypertension (Figure 1) or confirm the diagnosis of hypertension requiring treatment. Clearly I hope for the former, which would demonstrate that my previously recorded pressures were because of a white coat reaction that would merit annual review with an ABPM but no treatment, whereas the latter would dictate the necessity for drug treatment. Dissapointingly, the ABPM shows daytime pressure averaging 155/98 mmHg and nighttime pressures averaging 140/90 mmHg. I am given a prescription for a popular single pill combination (SPC) consisting of olmesartan 20 mg and hydrochlorothiazide (HCTZ) 20 mg, and I am asked to return for a repeat ABPM in 1 month.

Efficacy of Treatment

I take the medication, as prescribed, without any adverse effects. However, being aware that ABPM is available in several pharmacies in Ireland, I opt for this option rather than going back to my GP. The process is simple. I phone my local pharmacist for an appointment, attend at 9 AM on the appointed day, and return 24 hours later, at which time the pharmacist downloads the data from the monitor and presents me with a 1-page report that includes a plot of my ABPM and a computer-generated interpretative report. If the result is abnormal, the pharmacist will instruct me to make an appointment with my GP as soon as possible; if the result is normal, he will instruct me to bring it with me at my next GP attendance. Once again, there are 2 possible outcomes: my ABPM will either show 24-hour BP control or failure to attain control. Sadly, once again, my ABPM shows what I had been hoping against, lack of treatment efficacy. I bring the result to my GP who is pleased to learn of the pharmacy availability of ABPM, and he increases the olmesartan component in the SPC to 40 mg and the HCTZ to 25 mg.

A few weeks later, the above process is repeated, and once again the pharmacy ABPM, although slightly improved, shows that my BP remains elevated over the 24-hour. The next step is to add a calcium channel blocker to the SPC so that I am now taking olmesartan 40 mg, HCTZ 25 mg, and amlodipine 5 mg in a single pill once daily. A month later, ABPM is repeated and shows little improvement. Increasing amlodipine to 10 mg in the SPC, apart from causing some ankle swelling, has little

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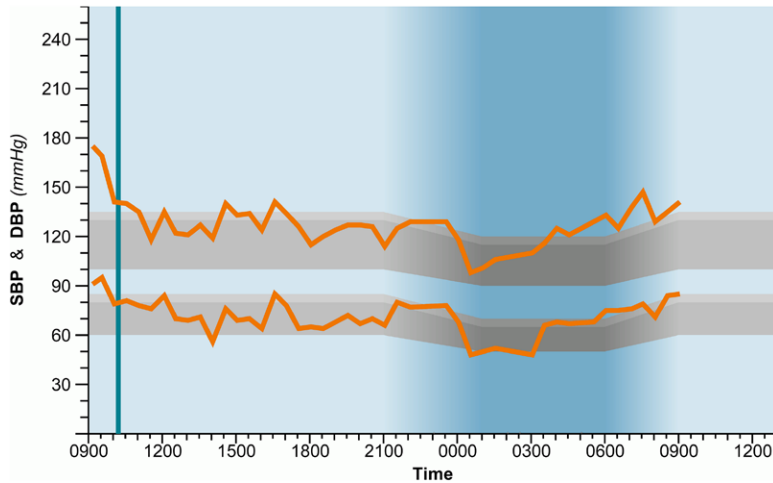


Figure 1. The ambulatory blood pressure measurement shows white coat hypertension (175/95 mmHg in first hour) with otherwise normal 24-hour systolic blood pressure (SBP) and diastolic blood pressure (DBP) (128/72 mmHg daytime and 117/61 mmHg nighttime).

effect on the next ABPM. Aware of the evidence for the inferiority of HCTZ in comparison with chlorthalidone (which is not available in Ireland)¹ and indapamide,² my GP replaces HCTZ with the latter but again with little improvement in ABPM.

Diagnosis of Resistant Hypertension

My GP, who is as disappointed as I am at the failure to obtain BP control asks me to discuss the problem with a colleague who has expertise in hypertension. His review confirms that I meet the criteria for a diagnosis of resistant hypertension.³ First, I can assure him that I have been fully compliant with treatment. Second, I have been on maximal doses of an angiotensin II receptor blocker, a calcium channel blocker, and thiazide-like diuretic, and, moreover, I have been on this treatment for for 2 months; the duration of treatment is often overlooked in the diagnosis of resistant hypertension.⁴ Finally, there is no evidence of secondary hypertension but, none-the-less, my colleague arranges for me to have a magnetic resonance angiogram of my renal arteries and estimation of urinary and serum catecholamines, all of which are normal. I must now accept the diagnosis of drug resistant hypertension, and the next step is to discuss the therapeutic options.

Therapeutic Options

Renal Denervation

Had my consultation taken place before January 9, 2014, the date of the press release by Medtronic stating that the trial on renal denervation for treatment-resistant hypertension, Symplicity HTN-3, (which it had sponsored) had failed to meet its primary efficacy end point of reducing systolic BP by 10 mmHg, and this procedure might have been considered, although concerns about the merit of the technique had been previously raised.⁵ However, with the full results of the trial now published,⁶ many thousands of patients may be asking if the early scientific studies had been properly designed, might they have been spared undergoing an ineffective (and costly) procedure that may not be without risk?^{7,8} So, clearly, renal denervation is not an option I would consider.

Renin Inhibitors

Renin inhibitors are the newest class of drugs introduced for the treatment of hypertension.⁹ After discussion, and a review of the somewhat inconclusive literature on aliskiren, we agree to leave this option for the future should such become necessary.¹⁰

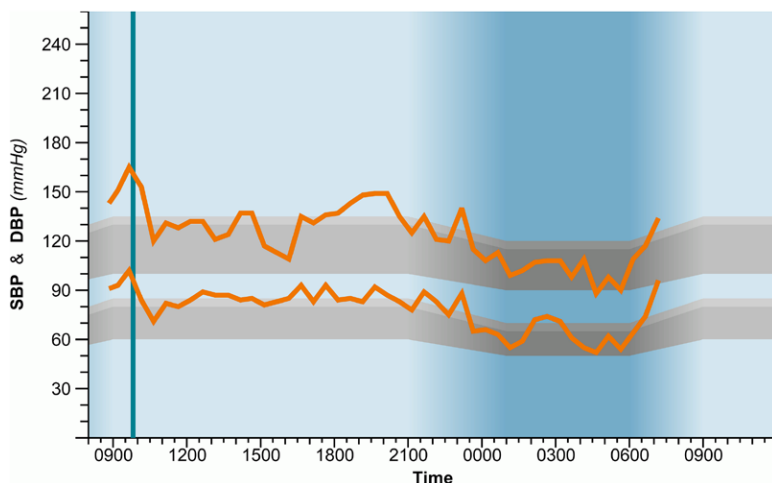


Figure 2. The ambulatory blood pressure measurement shows white coat hypertension (165/102 mmHg) with otherwise normal 24-hour systolic blood pressure (SBP) and diastolic blood pressure (DBP) (134/85 mmHg daytime, 101/62 mmHg nighttime). Plots and reports generated by dabl ABPM—© dabl 2014 (www.dabl.ie).

Aldosterone Antagonists

There is now growing evidence that resistant hypertension responds to aldosterone antagonists.¹¹ Spironolactone, in particular, has been shown to be particularly efficacious in patients resistant to other BP-lowering medication.¹² My colleague and I discussed the option of prescribing eplerenone as an alternative to spironolactone so as to avoid the potential adverse effect of painful gynecomastia, but, because there is evidence that eplerenone may not be as effective in lowering BP as spironolactone¹³ and because the former is much cheaper, we agreed to add spironolactone to my treatment in a dosage of 25 mg mane and to check my serum potassium after a week on treatment. After 2 weeks on spironolactone, I returned to my pharmacist for a repeat ABPM, which showed daytime pressures averaging 134/85 mm Hg and nighttime pressures 101/62 mm Hg (Figure 2). My treatment has subsequently been modified, without loss of 24-hour BP control, to an SPC containing olmesartan 20 mg, amlodipine 5 mg, and HCTZ 12.5 mg, along with spironolactone 25 mg and atorvastatin 20 mg daily.

Discussion

I have learned several lessons from my illness that may have some relevance for physicians faced with genuine resistant hypertension and, who knows, perhaps also for patients with the condition.

The first lesson is that adherence to treatment must be assured. Clearly, this was not an issue in my case, but the failure of patients to take prescribed medication is recognized as being a major cause for worldwide failure to achieve BP control.¹⁴ One of the most useful aspects of modern treatment, even for me, as a physician who should not be adverse to polytherapy, was the convenience of SPC medication, whereby it was possible for me to take 3 medications in 1 tablet but with the potential to increase olmesartan from 20 to 40 mg, amlodipine from 5 to 10 mg, and HCTZ from 12.5 to 25 mg.¹⁵ This advance in therapeutics must surely be a significant factor in achieving adherence to treatment when multiple drugs are required.

It is now generally accepted that a white coat reaction must be excluded with ABPM before making a diagnosis of resistant hypertension. Relying on conventional BP measurement will lead to a spurious diagnosis in $\approx 20\%$ of patients.¹⁶ Having been an advocate of ABPM for >30 years,¹⁷ it is also hardly surprising that I would insist on ABPM to determine the efficacy or, as the case was, failure of the treatment. What may be surprising, however, to many readers is that after having an initial ABPM performed in one of the many private clinics that provide this service in Dublin, I opted thereafter to have ABPM performed in my local pharmacy. My reasons for so doing were based on several considerations. First, pharmacy-based ABPM has been shown to be similar to doctor-provided ABPM, especially in that patients attending a pharmacy have the same prevalence of white coat hypertension as those attending a GP.¹⁸ Second, attending my local pharmacist saved me some 2 hours of what is for me valuable time that had been wasted between my GP and the private clinic. Third, the cost of attending my local pharmacist was about a quarter of the cost of attending a private clinic and my GP. Fourth, my pharmacist gave me

what my GP simply never had the facility to provide, namely a printout of my ABPM on 1 page with a plot of the 24-hour measurements superimposed on the normal bands, a summary of measurements in the white coat, daytime and night time windows, and a computer-generated interpretative report. When I had attended my pharmacist for >1 ABPM, he was able to provide me with a trend report of previous ABPM recordings that clearly showed if BP control was being achieved or not. If I were poorly compliant with prescribed medication, it would be obvious to me that BP control might be improved by the simple expedient of taking medication.

The therapeutic lesson I learned from my experience was the remarkable efficacy of spironolactone, which should surely be one of the prerequisite drugs to be prescribed before the diagnosis of resistant hypertension is made. There is also a good case for spironolactone to be a component of SPC drugs that are becoming increasingly available. Despite the substantial literature supporting the efficacy of aldosterone antagonists in the management of hypertension, one suspects that it is not much used in practice.

Historical Perspective

Finally, and by way of assessing changing times, I indulged myself by looking back to an article I wrote in 1978 for the *British Medical Journal* entitled "If I had hypertension" to introduce a series of articles on that theme.¹⁹ This article was written 5 years before I began to explore ABPM as a measurement technique for the management of hypertension¹⁷ and 10 years before Tom Pickering gave us the concept of white coat hypertension.²⁰ Interestingly, the article questions the reliability of conventional BP measurement in labeling me as hypertensive: "On the other hand, it is possible that the condition has been misdiagnosed... I would point to works showing the effects of stress and exertion on the blood pressure. I would even want to know if the good doctor's sphygmomanometer was accurate. Did he not use an aneroid model which has to be checked for accuracy from time to time (and so rarely is), and has it not been shown that about one-third of hospital sphygmomanometers are inaccurate for one reason or another?"¹⁹ And finally a plea for what we now call out of office BP: "I would ask [my doctor's] permission to take my own blood pressure two or three times weekly, a simple exercise which should help us both, and one which must surely come to have more universal application in managing hypertension."

And how much we have advanced with therapeutic options. In 1978, the options for treatment were "As I see it there are two possibilities: a thiazide diuretic alone, or with beta-blockers."¹⁹

This historical reminiscence is instructive. It should remind us how fortunate we are as practicing physicians to be heirs to remarkable technological advances in the 35 years since the article was written. We now have at our disposal accurate and sophisticated devices that record ABPM and home BP, along with centrally hosted software and databases that allow us to store and analyze a profound amount of data. Furthermore, we are privileged in having some 4 classes of drugs over and above the diuretics and β -blockers that were available in 1978. We must ask ourselves, therefore, if we have done justice to the advances that pharmacological and technological science

has bestowed on us? Sadly, the answer has to be an indictment of our scientific acumen. Why have we not made ABPM universally available to the public with hypertension and why have we not established registries capable of analyzing data to demonstrate poor control of BP in hypertensive subjects and to direct management so as to effect more efficient BP lowering? The methodology is available but the will to use technology is lacking. Why is it that the rule of halves exists in most countries with some 50% of the hypertensive population not achieving optimal BP control?²¹ The answer to this question can be addressed from many viewpoints, but I hope I have shown that ready access to ABPM would at least allow doctors, and importantly also their patients, to determine if BP control is being achieved with prescribed medication. I hope I have also shown that the wider use of SPCs provides us with a means of prescribing ≥ 2 drugs in a formulation that is acceptable to patients. If these lessons are debated, the cathartic purpose of this series will have been worthwhile.

Disclosures

E. O'Brien is a shareholder of dabl Ltd, Ireland.

References

- Dorsch MP, Gillespie BW, Erickson SR, Bleske BE, Weder AB. Chlorothalidone reduces cardiovascular events compared with hydrochlorothiazide: a retrospective cohort analysis. *Hypertension*. 2011;57:689–694.
- Akram J, Sheikh UE, Mahmood M, Donnelly R. Antihypertensive efficacy of indapamide SR in hypertensive patients uncontrolled with a background therapy: the NATIVE study. *Curr Med Res Opin*. 2007;23:2929–2936.
- de la Sierra A, Segura J, Banegas JR, Gorostidi M, de la Cruz JJ, Armario P, Oliveras A, Ruilope LM. Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. *Hypertension*. 2011;57:898–902.
- Turner JR, O'Brien E. Diagnosis and treatment of resistant hypertension: the critical role of ambulatory blood pressure monitoring. *J Clin Hypertens (Greenwich)*. 2013;15:868–873.
- Persu A, O'Brien E, Verdecchia P. Use of ambulatory blood pressure measurement in the definition of resistant hypertension: a review of the evidence [published online ahead of print April 17, 2014]. *Hypertens Res*. doi: 10.1038/hr.2014.83. <http://www.nature.com/hr/journal/vaop/ncurrent/full/hr201483a.html>. Accessed July 25, 2014.
- Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, Leon MB, Liu M, Mauri L, Negoita M, Cohen SA, Oparil S, Rocha-Singh K, Townsend RR, Bakris GL; SYMPLICITY HTN-3 Investigators. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med*. 2014;370:1393–1401.
- Fadl Elmula FE, Hoffmann P, Larstorp AC, Fossum E, Brekke M, Kjeldsen SE, Gjønnæss E, Hjørnholm U, Kjaer VN, Rostrup M, Os I, Stenehjem A, Høieggen A. Adjusted drug treatment is superior to renal sympathetic denervation in patients with true treatment-resistant hypertension. *Hypertension*. 2014;63:991–999.
- Templin C, Jaguszewski M, Ghadri JR, Sudano I, Gaehwiler R, Hellermann JP, Schoenenberger-Berzins R, Landmesser U, Erne P, Noll G, Lüscher TF. Vascular lesions induced by renal nerve ablation as assessed by optical coherence tomography: pre- and post-procedural comparison with the Simplicity catheter system and the EnligHTN multi-electrode renal denervation catheter. *Eur Heart J*. 2013;34:2141–2148, 2148b.
- Stanton A, Jensen C, Nussberger J, O'Brien E. Blood pressure lowering in essential hypertension with an oral renin inhibitor, aliskiren. *Hypertension*. 2003;42:1137–1143.
- Angeli F, Reboldi G, Poltronieri C, Angeli E, De Filippo V, Crocetti A, Bartolini C, D'Ambrosio C, Verdecchia P. Efficacy and Safety Profile of Aliskiren: Practical Implications for Clinicians. *Curr Drug Saf*. 2014; Feb 10. [Epub ahead of print] PubMed PMID: 24517108.
- Pimenta E, Calhoun DA. Treatment of resistant hypertension. *J Hypertens*. 2010;28:2194–2195.
- Václavík J, Sedlák R, Plachy M, Navrátil K, Plásek J, Jarkovsky J, Václavík T, Husár R, Kociánová E, Táborsky M. Addition of spironolactone in patients with resistant arterial hypertension (ASPIRANT): a randomized, double-blind, placebo-controlled trial. *Hypertension*. 2011;57:1069–1075.
- Parthasarathy HK, Ménard J, White WB, Young WF Jr, Williams GH, Williams B, Ruilope LM, McInnes GT, Connell JM, MacDonald TM. A double-blind, randomized study comparing the antihypertensive effect of eplerenone and spironolactone in patients with hypertension and evidence of primary aldosteronism. *J Hypertens*. 2011;29:980–990.
- Matsumura K, Arima H, Tominaga M, Ohtsubo T, Sasaguri T, Fujii K, Fukuhara M, Uezono K, Morinaga Y, Ohta Y, Otonari T, Kawasaki J, Kato I, Tsuchihashi T; Comfort Investigators. Impact of antihypertensive medication adherence on blood pressure control in hypertension: the COMFORT study. *QJM*. 2013;106:909–914.
- Dolan E, O'Brien E. Blood pressure variability: clarity for clinical practice. *Hypertension*. 2010;56:179–181.
- O'Brien E, Parati G, Stergiou G, Asmar R, Beilin L, Bilo G, Clement D, et al; on behalf of the European Society of Hypertension Working Group on Blood Pressure Monitoring. European Society of Hypertension Position Paper on Ambulatory Blood Pressure Monitoring. *J Hypertens*. 2013;31:1731–1767.
- O'Brien E, O'Malley K. Overdiagnosing hypertension. *BMJ*. 1988;297:1211–1212.
- James K, Dolan E, O'Brien E. Making ambulatory blood pressure monitoring accessible in pharmacies. *Blood Press Monit*. 2014;19:134–139.
- O'Brien E. If I had hypertension. *Br Med J*. 1978;1:1469–1470.
- Pickering TG, James GD, Boddie C, Harshfield GA, Blank S, Laragh JH. How common is white coat hypertension? *JAMA*. 1988;259:225–228.
- Kotchen TA. Hypertension control: trends, approaches, and goals. *Hypertension*. 2007;49:19–20.