



Refractory hypertension: overcoming hard to control blood pressure

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Refractory hypertension must be carefully differentiated from hypertension caused by other treatable conditions or poor compliance. Once diagnosed, it can be treated with several pharmacological options and specialist assistance.

Arterial hypertension is a complex disease with interplay of many physiological factors. The combination of an ageing population and increasing incidences of obesity and diabetes in younger age groups is contributing to a greater prevalence of hypertension in the population.¹ This has been followed by an increase in the number of patients with 'refractory' (or 'resistant') hypertension – that is, hypertension that does not respond to lifestyle modification and multiple blood pressure-lowering agents at maximal dose and is in the absence of a reversible cause. These patients have significant mortality and morbidity when their hypertension is left uncontrolled. To overcome the resistance to therapy, GPs need to consider the possible pathophysiology of hypertension in each patient.

This article focuses on refractory hypertension; the diagnosis and treatment of basic hypertension has been reviewed in several articles published in *Medicine Today*.²⁻⁴

Case scenario

A 78-year-old woman presents with a blood pressure (BP) of 182/91 mmHg despite maximal doses of perindopril, indapamide and amlodipine. She has always been compliant with her medications. She walks every morning for at least 30 minutes, is a lifelong nonsmoker, drinks no alcohol and uses no added salt at the table.

Epidemiology and description

The American Heart Association defines hypertension as refractory if, in the setting of adherence to lifestyle modification and at least three drugs (including a diuretic) at maximal doses, BP has not reached the target levels of below 140/90 mmHg for low-risk individuals or below 130/80 mmHg for high-risk individuals.⁵ Use of at least three antihypertensive drugs is now commonplace for the treatment of many hypertensives, and clinical trials had always demonstrated that this was common in their study populations.

Key points

- Refractory hypertension, defined as blood pressure that remains high despite lifestyle modification and three antihypertensive medications, appears to be increasing in prevalence.
- Refractory hypertension must be differentiated from otherwise poorly controlled hypertension by examining lifestyle factors (including hypertension-inducing drugs), treatment compliance and potential secondary causes of hypertension, such as renal disease and obstructive sleep apnoea.
- An important diagnostic tool for diagnosing true refractory hypertension versus white coat hypertension is 24-hour blood pressure monitoring.
- Treatment of refractory hypertension comprises strict diet and lifestyle modifications along with more aggressive pharmaceutical measures, such as maximising diuretic therapy, using combination therapies and considering use of novel therapies. Referral of patients to a specialist hypertension clinic and regular biochemical monitoring may be required.

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For example, one-third of patients in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) were receiving three or more antihypertensive agents.⁶ Similarly, in the Second Australian National Blood Pressure (ANBP2) study, 48% of the treated hypertensive group in an elderly population still had readings greater than 140/90 mmHg on screening.⁷ The Reduction of Atherothrombosis for Continued Health (REACH) database has shown that over 30% of patients fail to reach the BP targets suggested by the International Society of Hypertension Guidelines (Figure 1).⁸

Although this definition of refractory hypertension was recently clarified in the American Heart Association guidelines, the overwhelming confounder to allowing the true incidence of refractory hypertension to be discovered is that hypertension is treated poorly in the community for a myriad of reasons and hypertension is commonly mislabelled as refractory. Difficult-to-control hypertension is related to several factors,

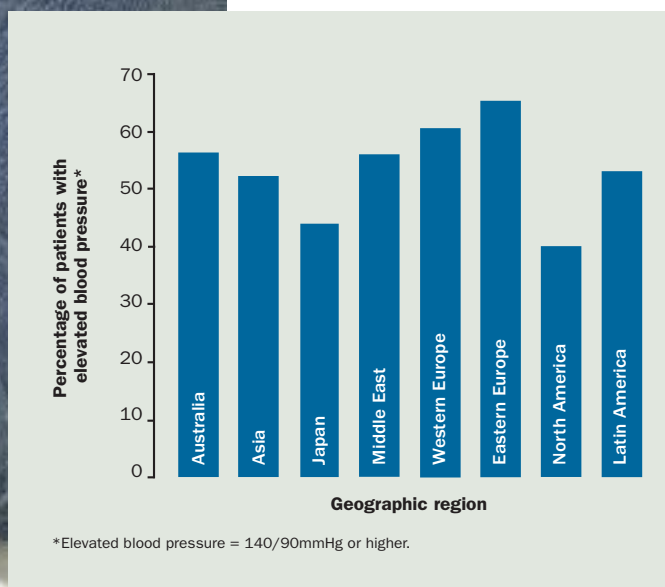


Figure 1. Patients with hypertension are not achieving treatment targets worldwide. Almost all the Australian patients in the REACH Registry who had elevated blood pressure were taking one or more antihypertensive agents yet more than half were not at their treatment goal. (Adapted from Bhatt et al. *JAMA* 2006; 295: 180-189.)⁸



Figure 2. A diagnosis of refractory hypertension begins with the exclusion of pseudo resistance. Use of 24-hour ambulatory BP monitoring enables accurate measurement of blood pressure fluctuations and often reveals the anxiety-related hypertension some patients have when attending clinics – the ‘white-coat-effect’.



including doctor inertia, poor patient adherence, doctor–patient miscommunication, inappropriate BP measurement and inadequate antihypertensive interventions. This leads to uncontrolled hypertension, not refractory hypertension, although both groups of patients are at increased risk of a cardiovascular event.

Refractory hypertension is likely to be rising in prevalence, although no epidemiological or clinical study (using titration tablet methods of blood control) exists to show this rise. Suggestion of an increasing prevalence is derived from the proportion of patients with uncontrolled hypertension in recent studies. In a Spanish cohort of patients with hypertension, 12% had inadequate BP control despite all maximal therapeutic attempts.⁹

Refractory hypertension has consequences. It is seen as a failure by the clinician, who may accept the ongoing poor control or refer the patient to a cardiologist, renal physician or specialist clinic for further management. In the Reassessment of Antihypertensive

Chronic Therapy (REACT) study, for example, 42% of physicians decided not to modify the antihypertensive regimen, even though their patients’ hypertension was not controlled after more than one year of follow up.¹⁰ Many such patients require further evaluation and consideration of different therapeutic (pharmacological and nonpharmacological) measures.

Case scenario continued

The patient has had probable refractory hypertension demonstrated on 24-hour ambulatory monitoring, but secondary causes need exclusion. She has elevated daytime and night-time BP, averaging 175/95 mmHg by day and 160/70 mmHg at night.

Exclusion of pseudo resistance

The diagnosis of refractory hypertension should begin with the exclusion of pseudo resistance (blood pressure that is only elevated in the presence of usually medical staff taking it; in a nonclinical environment, blood pressure is within target levels). The identification of various factors characteristically found in patients with hard to control hypertension, and their treatment (if applicable), should be the first step (see the box on this page).

Fluctuations in blood pressure can be measured accurately using 24-hour ambulatory BP monitoring (Figure 2), although interpretation of the results is complex.⁴ The use of 24-hour monitoring often reveals the anxiety-related hypertension that patients have when attending clinics – the ‘white-coat effect’. In a study published in 2001, the use of ambulatory BP monitoring enabled the detection of true refractory hypertension in approximately 2% of all hypertensive outpatients referred to that hypertension unit.¹¹

Exclusion of noncompliance

Medications for hypertension have predictable adverse reactions that often lead to noncompliance. The existence of noncompliance to medication is well known. In a recent study from a large database in Australia, 19% of patients failed to collect the second script for their antihypertensive agent.¹² Analysis demonstrated relative differences in compliance between medications – better for angiotensin receptor blockers versus calcium channel blockers – but in reality there was extensive noncompliance in many groups and this would have a presumed effect on the reaching of target blood pressures for patients.

Case scenario continued

The patient has multiple health issues, including obesity (body mass index, 31 kg/m²), type 2 diabetes, a lowered estimated glomerular filtration rate (56 mL/min) and proteinuria (1+ protein on urine dipstick). She was not noted to have sleep disturbance, heavy snoring or apnoeas.

Exclusion of secondary hypertension

The next diagnostic step is to exclude a secondary cause of hypertension.² The most common causes are renal parenchymal disease, small and large vessel renal artery disease, obstructive sleep apnoea

Characteristics of patients with true refractory hypertension

- Older age (over 65 years)
- Obesity
- Chronic kidney disease
- Diabetes
- Black race (African American)
- Female sex
- Obstructive sleep apnoea
- Excessive salt ingestion (more than 12 g/day)^{4*}
- Drugs (NSAIDs, cyclosporin, corticosteroids)
- Secondary hyperaldosteronism from multiple medications for hypertension

* Target salt intake: aim for less than 6 g/day.



and hyperaldosteronism. Patients who are obese have higher blood pressure, and use of excessive alcohol and salt intakes greater than 12 g a day also lead to excessive blood pressure. It is always important to investigate primary aldosteronism in patients with previously stable hypertension that has become unstable and refractory. The incidence of this appearance of hyperaldosteronism seems to be as high as 10 to 20% of 'refractory' hypertension studies in the literature.¹³⁻¹⁵ Additionally, there is the possibility of renal vascular disease as a cause of secondary hypertension, although medical therapy is now the optimal treatment in all but a few selected cases.¹⁶

Sleep apnoea is now being recognised as a possible cause of poorly controlled hypertension, and patients should be assessed for the presence of this condition. Numerous studies have demonstrated that effective diagnosis and treatment of sleep apnoea can improve mild-to-moderate hypertension and refractory hypertension.¹⁷

Case scenario continued

The patient was not taking any medications, including herbal medicines, that would be considered prohypertensive. As mentioned earlier, the patient has always been compliant with her medications, walks every morning for at least 30 minutes, is a lifelong nonsmoker, drinks no alcohol and uses no added salt at the table.

Exclusion of drug-induced hypertension

Another possible aetiology of refractory hypertension is drug-induced hypertension. As well as many prescribed drugs causing increased BP, numerous commonly used over-the-counter medications and illicit drug use can also have a hypertensive effect (see the box on this page).

NSAIDs (e.g. COX-2 inhibitors) and sympathomimetic agents, including anorectics, appear to be the most frequent causes of drug-induced sustained BP elevation. Cocaine, amphetamines and other illicit drugs can also be contributors. Other potential substances that

Nonprescription causes of elevated blood pressure		
Over-the-counter medications		
NSAIDs	Nasal decongestants	
Cold and flu remedies		
Herbal medications		
Aniseed	Chasteberry	Guarana
Bayberry	Cola alkaloids	Liquorice
Blue cohosh	Coltsfoot	Parsley
Broom alkaloids	Ephedra	Pau d'arco
Calamus	Gentian	St John's wort
Capsicum	Ginseng	Vervain
Illicit drugs		
Methamphetamine	Amphetamine ('speed')	
Cocaine		

may render the treatment of hypertension more difficult include the herbal constituents listed in the box below, energy drinks, androgens and anabolising hormones. Immunosuppressant agents (e.g. cyclosporin) should also be considered as potential causes of refractory hypertension. The mechanisms behind these drugs' effects include vascular tone changes, salt and water retention with volume expansion and abnormal activation of sympathetic tone.

Lifestyle modification

Not surprisingly, the last modifiable risk factor, and often the one with the most therapeutic nihilism, is lifestyle, including diet. Data have existed for decades that exercise, reduced alcohol intake and a low-salt (low-sodium) diet are effective in lowering BP.¹⁸

The typical Western diet has excessive intakes of sodium and fat, both of which have renal and central effects. Reducing sodium and fat intakes is, therefore, appropriate to help achieve therapeutic targets. As well, reversal of a sedentary lifestyle has demonstrable benefits.

Thus, as a fundamental step in the treatment of any patient with refractory hypertension, clinicians must reinforce appropriate lifestyle interventions of sodium restriction, weight loss, physical activity, smoking cessation and moderation of alcohol intake.

Treatment of refractory hypertension

Pharmacological treatment

The medical management of refractory hypertension includes:

- the maximising of diuretic therapy, including possible addition of aldosterone blockade (spironolactone), while monitoring potential electrolyte disorders through regular biochemical assessment, including serum potassium and sodium levels
- the concurrent use of agents with different mechanisms of action – for example, ACE inhibitors or angiotensin II receptor blockers (ARBs) with calcium channel blockers; these drug combinations are often available as fixed-dose formulations
- the use of centrally-acting sympatholytic blockers (moxonidine, the α -agonists clonidine and methyldopa, and cardioselective β -blockers such as atenolol and metoprolol)
- consideration of the use of novel therapies, including nonpharmacological methods of BP control.

Diuretic therapy maximisation

Maximisation of diuretic therapy is a very useful tool, but is often neglected due to clinical inertia or fear of side effects, including hypokalaemia and dysglycaemia. Progressive salt accumulation and the associated fluid retention often leads to refractory hypertension. The possibility of subclinical hypervolaemia should be carefully considered in each patient with persistently elevated BP.

The use of aldosterone antagonists is now a well-established therapy for refractory hypertension, even when there has been no clinical or biochemical identification of true hyperaldosteronism.¹ Spironolactone is a very effective BP-lowering agent but is underutilised due to its potential adverse effects, especially among men and

older people (rash, diarrhoea and, in men, gynaecomastia). In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), spironolactone had a large usage and was able to reduce systolic BP levels from 157/85 mmHg to 135/76 mmHg.¹⁹ It also has an emerging role, particularly for patients with sleep apnoea and hypertension.

The newer generation aldosterone antagonist eplerenone does not have same side effects due to its specificity but it is not available through the PBS for treatment of hypertension. Amiloride may be another potential option, as it inhibits the final pathway that aldosterone acts on.

Combination therapy

It is well recognised that more than one antihypertensive agent is usually required to control BP, and it has been shown that a combination of medications such as an ACE inhibitor or ARB with a thiazide or calcium channel blocker yields improved outcomes. Since the results of studies such as ASCOT and Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) have been available, fixed-dose combination therapy (at multiple dose levels) has been used.^{19,20}

Whether through better compliance or the concept that two long-acting drugs are having a synergistic effect, this therapeutic strategy has led to better control in patients with difficult to treat hypertension (80 to 90% of responders in the combined data).

Older agents, direct renin inhibition, higher potency drugs and new agents

Centrally-acting sympatholytic drugs such as clonidine and methyl-dopa are effective agents but have significant side effects. The newer drugs in this class, such as moxonidine, are generally better tolerated.

A new direct renin inhibitor, aliskiren, now licensed in the USA, has failed to significantly affect treatment of hypertension as it is no more potent than an ACE inhibitor or ARB and has a similar side effect profile to ARBs.²¹

Minoxidil, a potent vasodilator, lowers BP very effectively but causes troublesome hirsutism among women and marked fluid retention. It can be considered as an additional medication for true refractory hypertension but its use should be monitored by a specialist hypertension clinic.

Fourth-line agents often used with some success include β -blockers and high-dose α -blockers (the latter act as peripheral vasodilators).

All these approaches have been shown in numerous small studies to have efficacy. On the horizon are aldosterone synthase inhibitors, endothelin antagonists and endopeptidase inhibitors.²²

Nonpharmacological treatment of refractory hypertension

The first significant study of nonpharmacological management of BP was published recently in *The Lancet*.²³ In this multicentre randomised controlled trial, treatment comprised endovascular radiofrequency ablation of the sympathetic nerves in the renal arteries, and 80% of the treated group were able to achieve significant

Refractory hypertension: basic steps of management

- Exclude pseudo resistance and noncompliance using 24-hour ambulatory BP monitoring and compliance indicators
- Screen for secondary hypertension, including drug-related and obstructive sleep apnoea
- Attempt aggressive diet and lifestyle modification
- Maximise diuretic therapy
- Add combination agents to maximise pharmacological effect and compliance
- Add centrally-acting sympatholytic agents
- Refer to a hypertension specialist for consideration of new pharmacological agents and novel nonpharmacological therapies

BP reduction. The applicability of this technique in clinical practice is still to be demonstrated.

Early data are also available on the efficacy, safety and tolerability of implantable pulse generators in experimental and human studies.²⁴ This system consists of surgically and chronically implanted pulse generator and bilateral perivascular carotid sinus leads, and is being evaluated in prospective clinical trials for the treatment of drug-resistant hypertension.

Conclusion

Refractory hypertension must be differentiated from poorly controlled hypertension before more pharmacological treatment of the condition is considered. Pseudo resistance and medication non-compliance should be excluded by the use of 24-hour ambulatory BP monitoring and compliance indicators, any secondary causes of hypertension should be identified and treated, and strict diet and lifestyle modifications should be trialled.

Maximising diuretics, particularly spironolactone, and the use of sympatholytic approaches have good efficacy. Fixed-dose combination therapies are now available and have been shown to improve compliance and reduce pill burden and cost as well as improve control. For a summary of the management of refractory hypertension, see the box on this page.

In the future, these patients with drug-resistant hypertension may best be treated by nonpharmacological interventions such as radioablation of sympathetic nerves in the renal arteries and implantable pulse generators, but time will show whether these exciting techniques provide a 'cure' for refractory hypertension. **CT**

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A list of references is available on request to the editorial office.

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