

Resistant hypertension: an approach to management in primary care

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ABSTRACT

Hypertension is widely encountered in family medicine. Despite its prevalence, many patients have uncontrolled or difficult-to-control blood pressure. Resistant hypertension is defined as hypertension that is poorly responsive to treatment and requires the use of multiple medications to achieve acceptable blood pressure ranges. It may be a consequence of secondary hypertension or have no identifiable cause. Resistant hypertension is important to recognise because it places patients at risk of end-organ damage. Primary care physicians should be aware of the therapeutic approach for hypertension when traditional therapy fails. This article aims to familiarise readers with the evaluation and management of resistant hypertension by outlining the most recent evidence-based treatment options.

Keywords: Blood pressure, cardiovascular disease, renal denervation, resistant hypertension

Introduction

Hypertension is defined as persons 18 years of age and over with a systolic pressure reading of 140 mmHg or more or a diastolic reading of 90 mmHg or more, or those taking antihypertensive medications.^[1,2] Between 90-95% of cases are essential hypertension in which there is no identifiable cause.^[3] The remaining cases of hypertension are secondary to a distinguishable process and would likely resolve if the underlying condition was treated.

A considerable number of patients fail to reach target blood pressure ranges despite lifestyle advice and standard medical therapy. Resistant hypertension is defined as blood pressure that remains above 140/90 mmHg despite use of three antihypertensive medications of different classes at the best tolerated doses, one of which must be a diuretic.^[4,5]

Epidemiology

Hypertension is widely encountered in primary care and is the most common condition managed at primary care level.^[1] It accounts for 8.6% of all visits to a primary care physician.^[2] Hypertension affects 32% of adults in western society, two-thirds

of whom are poorly controlled.^[6,7] Its prevalence is likely to continue rising.^[8]

It is estimated that approximately 10% of hypertensive patients in westernised countries have resistant hypertension.^[9,10] Doctors in primary care can expect to encounter resistant hypertension one in every 20 hypertensive patients, compared with higher rates in specialist clinics.^[10]

Aetiology and pathogenesis

In most cases the pathogenesis of resistant hypertension is uncertain. Only in a minority of instances is the problem due to secondary hypertension. In the absence of a secondary cause the condition is most likely multifactorial. Proposed mechanisms include genetic factors, aberrant sympathetic nervous system activation and altered renal sodium and water handling due to changes in the renin-angiotensin-aldosterone system.

Clinical features and diagnosis

Although hypertension is usually asymptomatic detection and treatment remains important. Uncontrolled blood pressure is a considerable cardiovascular risk factor that makes target-organ damage more likely.^[11] Possible end-organ consequences of untreated hypertension include heart failure, stroke, ischemic heart disease and renal failure.

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Resistant hypertension presents in patients who have persistently elevated blood pressure which responds minimally to therapy. Approximately six months of treatment with three conventional antihypertensive agents should be allowed for at least some blood pressure correction.^[9] If at six months treatment is proving unsuccessful the possibility of resistant hypertension may be contemplated.

The true prevalence of resistant hypertension is difficult to quantify because many patients actually suffer ‘pseudo-resistant’ hypertension. Pseudo-resistant hypertension refers to poorly controlled disease which appears resistant but is actually attributable to other factors. The commonest reasons for apparent treatment resistance are medication non-compliance and insufficient drug therapy. Other implicated factors include failure to adhere to lifestyle advice, poor measurement technique, white-coat hypertension and the use of medications that interfere with blood pressure [Table 1].

A key step in diagnosing resistant hypertension is confirming that blood pressure elevation is truly resistant. Pseudo-resistance must be ruled out with a thorough history and medication review, followed by measurement of blood pressure with proper technique. Provided these confounders are absent and standard drug therapy has failed, resistant hypertension is diagnosed.

Every patient with resistant hypertension requires at least some screening for secondary causes [Table 2]. Obstructive sleep apnoea, chronic kidney disease and primary hyperaldosteronism are the most frequent comorbidities.^[12] Although secondary hypertension is more likely in resistant hypertension than in patients whose blood pressure is controlled, most still do not have an identifiable cause.^[13]

Evaluation for secondary causes should include comprehensive history and physical examination searching for any clues pointing towards to an underlying diagnosis. For example the patient may have symptoms of obstructive sleep apnoea, or alternatively episodic palpitations with headaches and diaphoresis might suggest pheochromocytoma, while an abdominal bruit could indicate renal artery stenosis. Oftentimes however, the clinical assessment will be unremarkable.

Beyond history and examination, all patients with resistant hypertension should be investigated at minimum with a serum creatinine test, estimated glomerular filtration rate and urine dipstick.^[10] This is due to the high prevalence of chronic kidney disease in this population. Any derangement in these baseline investigations warrants a renal ultrasound scan.^[10] It is also advisable to order serum sodium, potassium and glucose because the test is simple and often helpful. Because of the confounding nature of the white-coat effect, 24-hour ambulatory blood pressure monitoring should also be undertaken.^[11,14,15] Pressure readings from ambulatory monitoring correlate more closely with morbidity and mortality than measurements obtained in clinic.^[14]

Further screening investigations for secondary causes are not compulsory. Additional tests [Table 3] should be chosen depending on the clinical circumstances of the patient as revealed by history and examination.

Finally, all patients with ongoing uncontrolled hypertension should be assessed routinely for any signs of end-organ compromise. This may include measures such as yearly fundoscopy, electrocardiogram and urine dipstick.

Management

Primary care physicians are familiar with the management of essential hypertension. Treatment should comprise both lifestyle modification and pharmacologic therapy. The blood pressure goal in uncomplicated patients is 140/90 mmHg which could be relaxed to 150/90 in patients greater than 60 years of age.^[17] A more appropriate treatment target in patients with end-organ damage is 130/80 mmHg.^[5,15]

Non-pharmacological treatment

Non-pharmacologic measures should be introduced in patients with hypertension of any severity. Recommendations include

Table 1: Drugs that interfere with blood pressure control^[10]

Non-steroidal anti-inflammatories
Oral contraceptives
Corticosteroids
Tricyclic antidepressants
Monoamine oxidase inhibitors
Other substances-caffeine, cocaine, alcohol

Table 2: Causes of secondary hypertension^[10]

Chronic kidney disease
Renovascular disease
Obstructive sleep apnoea
Coarctation of the aorta
Pheochromocytoma
Primary hyperaldosteronism
Cushing’s syndrome
Thyroid disease
Intracranial mass

Table 3: Initial investigations for suspected causes of secondary hypertension^[10,16]

Disorder	Suggested investigation
Primary hyperaldosteronism	Plasma aldosterone: Renin ratio
Thyroid disease	Thyroid function tests
Pheochromocytoma	24-hour urinary catecholamine level
	Plasma metanephrines
Cushing’s syndrome	Urinary cortisol
Obstructive sleep apnoea	Polysomnography
Renovascular disease	Renal artery duplex scan
Renal parenchymal disease	Renal ultrasound scan
Coarctation of the aorta	Cardiac ultrasound scan

smoking cessation, reduction in alcohol intake, dietary sodium restriction, healthy eating plans, increased physical activity and weight loss. Lifestyle interventions complement the efficacy of drug therapy and, alone, are often satisfactory in uncomplicated essential hypertension.

Pharmacological treatment

There is little randomised trial data to guide choice of drug regimen for patients with resistant hypertension and recommendations are largely empirical. In general, the best strategy is to formulate a combination therapy that targets different physiological mechanisms and accounts for patient comorbidities.

The preferred initial drug choices are the same as for essential hypertension.^[18] The guidelines of the National Institute for Health and Clinical Excellence (NICE) recommend initial treatment with an angiotensin-converting enzyme inhibitor (ACE inhibitor) in patients younger than 55 years of age, or a dihydropyridine calcium channel blocker (CCB) in patients older than 55 or black patients of any age.^[19] These options can then be trialled in combination and titrated as necessary before adding a thiazide as the third medication.

Guidelines endorse commencement of antihypertensive treatment with only one drug because adequate monotherapy controls hypertension in 30% of cases.^[20] If monotherapy is insufficient the regimen could be modified depending on therapeutic effect by altering dose or adding an additional class of drug. Triple therapy must be optimised before selecting further add-on therapy because optimal dosing and drug selection can see blood pressure normalise in many patients.

Whatever regimen is chosen it is important that it be tailored to the individual patient. Comorbidities must be considered when selecting an antihypertensive agent. For instance, in patients over 55 years of age with evidence of heart failure a thiazide diuretic might be a more suitable first-line option than a CCB. Alternatively, if patients are intolerant to an ACEI because of cough it is acceptable to replace the ACEI with an angiotensin receptor blocker (ARB). This should achieve a comparable blood pressure lowering effect.

Most patients with hypertension are prescribed hydrochlorothiazide as the diuretic of choice. However, several recent clinical trials have demonstrated superior blood pressure reduction with chlorthalidone, especially in patients with resistant hypertension.^[20-24] Chlorthalidone is a thiazide-like diuretic with a longer half-life and greater potency than hydrochlorothiazide. A good initial step in controlling refractory hypertension is therefore to switch patients from hydrochlorothiazide to chlorthalidone. The starting dose of chlorthalidone is 12.5 mg daily, taken in the morning, titrated if necessary to a maximum of 50 mg daily.^[25,26]

Indapamide is an alternative thiazide-like agent which may be more suitable than chlorthalidone in some patients.

Chlorthalidone has a longer half-life and duration of action than indapamide and is associated with a higher risk of renal impairment and hypokalaemia. Thus in predisposed patients such as the elderly or those with renal insufficiency indapamide might be a superior substitute.^[27] An appropriate starting dose is a 1.5 mg controlled-release tablet each morning.^[19] Patients with severe renal impairment (GFR below 30 mls/min) should have their thiazide replaced by a loop diuretic under specialist guidance.^[12]

In some cases the drug regimen may be altered by having patients take one antihypertensive agent at night-time instead of conventional morning-only dosing. Blood pressure generally lowers physiologically during sleep and nocturnal hypertension, or so-called 'non-dipping', has been associated with poorer cardiovascular prognosis.^[28,29] There is recent trial data on resistant hypertension which suggests improved blood pressure reduction with fewer cardiovascular events if one antihypertensive is ingested nocturnally.^[30] Importantly, there is no significant difference in adverse outcomes with this approach.^[31] Therefore, shifting one agent to bedtime dosing is not an unreasonable decision in patients with resistant hypertension. However, if electing to trial nocturnal therapy it is generally wise to avoid a diuretic as the night-time medication.

Spirolactone is recommended as the fourth antihypertensive drug.^[12,32] The Scandinavian Cardiac Outcomes Trial (ASCOT) showed mean blood pressure reduction of 22/10 mmHg at one year follow-up in patients with resistant hypertension randomised to receive spironolactone as the fourth medication.^[27] A general rule is to commence patients on 25 mg per day, which may require about 2 weeks for full effect. This dose can be increased gradually, preferably over several months, to a maximum of 100 mg daily if necessary. Adverse effects of spironolactone usually appear at higher doses where patients may complain of gynecomastia and breast tenderness, menstrual irregularities and sexual dysfunction. Amiloride, a potassium-sparing diuretic, is a reasonable alternative in those intolerant of spironolactone. Its dose ranges from 2.5-10 mg daily. A caveat for both spironolactone and amiloride is the need for careful routine monitoring of serum potassium. If the blood potassium level exceeds 4.5 mmol/L intensification of thiazide therapy should be considered.^[33]

The dual renal-angiotensin-aldosterone system blockade offered by spironolactone with ACEIs is not matched by combining ACEIs with ARBs. The landmark Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) demonstrated no additional benefit between using ACEIs or ARBs alone and in combination.^[34] Treatment regimens therefore should not include both an ACEI and ARB simultaneously.

Difficult patients will require referral to a hypertension specialist. Indications for referral include patients with uncontrolled blood pressure despite receiving maximum tolerated doses of

four medications, patients suffering end-organ damage as a consequence of their high blood pressure, or patients with a suspected secondary cause [Table 4]. All patients unresponsive to quadruple therapy should be reevaluated for a secondary cause.

Most patients with resistant hypertension do achieve blood pressure control through pharmacotherapy provided they are properly evaluated and treated.^[35] Patients who remain hypertensive despite four agents can have additional medications trialled sequentially with direction from a specialist [Figure 1]. Drug selection must be stepwise with careful appraisal of clinical circumstances at each stage. Patient comorbidities often dictate medication choices and it is judicious to begin each medication at the lowest dose practicable. Occasionally these less-frequently used agents will require earlier introduction depending on clinical circumstances.

Vasodilating beta blockers, such as carvedilol and labetalol, are a preferable next option as fifth-line drug therapy.^[12] They are not recommended as first-line therapy for patients with uncomplicated hypertension because they offer less cardiovascular protection than other agents. For example, patients treated with beta blockers in the Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints (CONVINCE) trial had higher rates of stroke than with any of CCBs, ACEIs or thiazides.^[36] Carvedilol should be initiated at 12.5 mg daily for at least two days, before increasing by 12.5 mg every two weeks to a maximum dose of 50 mg per day. Labetalol is commenced initially at 100 mg twice daily and titrated to a maximum of 2.4 g daily. Labetalol must not be increased faster than by 200 mg increments per day. In some patients such as those with ischemic heart disease

or poor glycaemic control, traditional beta blockers like atenolol or metoprolol may instead be indicated. Their antihypertensive benefit is presumably smaller although head-to-head comparison data is lacking.^[12]

Other options include alpha blockers, clonidine, methyldopa and direct vasodilators such as hydralazine or minoxidil. These seldom form part of the routine management of hypertension and should be prescribed with expert advice. Although such agents are very efficacious in controlling blood pressure their use must be tempered by side effect profiles and the comorbidities of the patient [Table 5]. These medications have not been adequately studied in resistant hypertension and the choice of agent depends largely on patient situation and individual prescriber preference. Most clinicians tend to opt for centrally-acting agents before the direct vasodilator drugs because experience with their use is wider.

Interventional treatment

There is a need for alternative treatment strategies in refractory patients who remain hypertensive despite optimum medical therapy. Two potentially effective interventional therapies are currently being assessed for this purpose. These are renal denervation and carotid sinus stimulation.

Renal denervation (RD) is a minimally invasive percutaneous approach that involves placement of an electrode in the renal arteries followed by ablation of sympathetic nerves. Sympathetic innervation stimulates renin release from the juxtaglomerular apparatus and afferent vasoconstriction of renal vessels, both of which lead to increased tubular reabsorption of sodium and elevated blood pressure. Renal denervation is therefore based on the principle that deactivation of renal sympathetic nerves will curb hypertension.

Until recently, available data indicated that this procedure provides moderate blood pressure reduction in patients with resistant hypertension. This was demonstrated in several unblinded studies, including SYMPLICITY-HTN-2. That trial, conducted in centres across Australia, New Zealand and Europe,

Table 4: Indications for specialist referral in hypertensive patients^[9]

Suspected secondary hypertension
Hypertension with target-organ damage
eGFR <30ml/min/1.73m ²
eGFR decline of 15% within 3 months
Proteinuria >1g/day
Requiring >4 medications for pressure control [10,40]

Table 5: Specialised medication options for resistant hypertension^[25,32,37-40]

Drug class	Examples	Recommended dose	Notes
Alpha blockers	Prazosin	0.5 mg daily, initially nocte, increasing to maintenance dose of 1-10 mg twice daily	Useful option in men with benign prostatic hyperplasia and lower urinary tract symptoms Can cause postural hypotension so use with caution in elderly
Centrally acting sympatholytic	Clonidine Methyldopa	50 mcg twice daily, up to 300 mcg twice daily 125 mg twice daily initially, up to 250 mg twice daily	Adverse effects are relatively common with both agents, such as dry mouth and sedation Abrupt cessation of clonidine can cause severe rebound hypertension so must be weaned carefully Methyldopa is a safe non-teratogenic option in pregnancy and remains widely used in that setting
Direct vasodilators	Minoxidil Hydralazine	5 mg daily, up to 30 mg twice daily 12.5 mg daily, up to 200 mg daily in divided doses	Minoxidil commonly causes reflex tachycardia and fluid retention Minoxidil must be used cautiously in patients with heart failure and coronary artery disease Minoxidil requires co-administration of a beta blocker and loop diuretic to offset tachycardia and fluid retention Minoxidil causes hypertrichosis so should be avoided in women Hydralazine provides less antihypertensive effect but is also associated with fewer adverse effects Most clinicians familiar with their use elect hydralazine in women and minoxidil in men

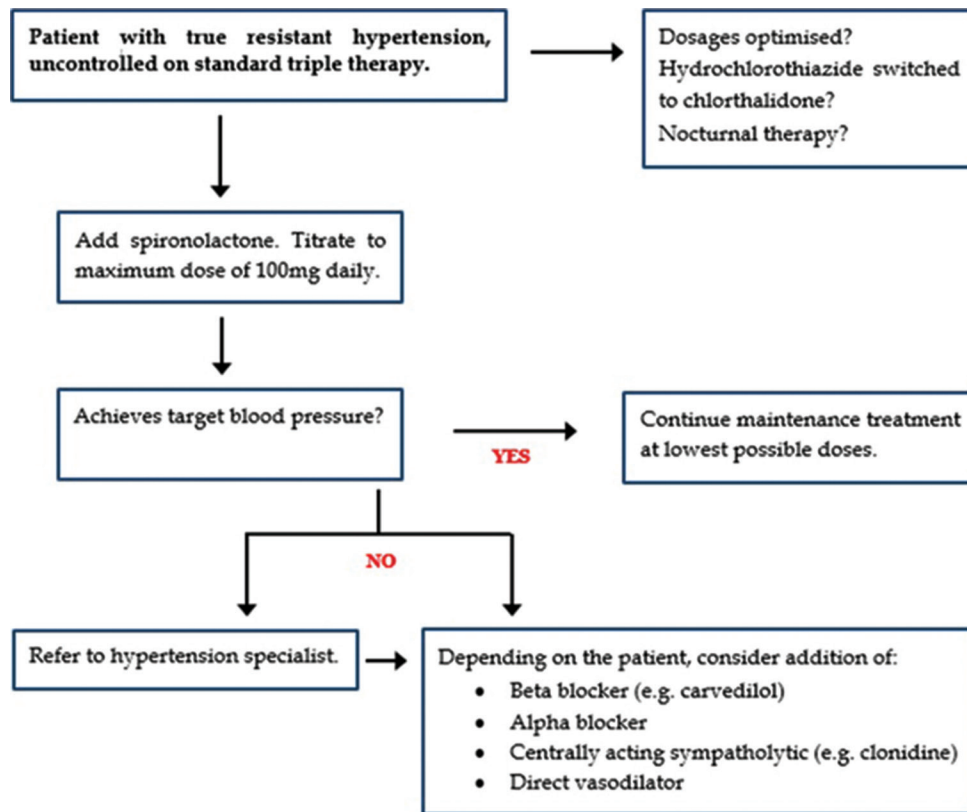


Figure 1: Stepwise pharmacologic management of resistant hypertension

demonstrated a mean pressure reduction of 32/11 mmHg at six months post-RD, and was not associated with any major complications.^[41]

However, a blinded randomised controlled trial released in April 2014, SYMPLICITY-HTN-3, failed to demonstrate any blood pressure benefit for RD versus a sham control procedure in 535 patients with resistant hypertension.^[42] This paper represents the most definitive evidence available to date, in contradiction to past studies, and therefore the utility of RD remains unestablished.

The other emerging intervention is carotid sinus stimulation. This is founded on the theory that continuous electrical stimulation of carotid baroreceptors, via an implantable device, should inhibit sympathetic output. Carotid baroreflex activation is a new procedure with limited experience. Although several feasibility studies have demonstrated appreciable pressure reduction the safety of this technique is not yet certain.

The Rheos Pivotal Trial is the only major double-blind randomised study published on carotid sinus stimulation. It reported substantial blood pressure reduction but was also associated with serious procedure-related adverse effects in 25.2% of participants.^[43] Complications were primarily related to nerve injury during device implantation though there was also a 2.3% incidence of hypertension-induced stroke. This event rate exceeds procedural safety allowances and is unsatisfactory.

Experience with carotid sinus stimulation is currently limited. Knowledge of device safety and long-term efficacy remains insufficient and it is not a routinely available management option at this time.

Conclusion

Hypertension is a challenging clinical problem with a significant proportion of patients failing to achieve blood pressure control despite extensive medical therapy. Resistant hypertension is defined as blood pressure that remains above 140/90 mmHg despite optimal use of three antihypertensive medications of different classes, including a diuretic. Such patients are more likely to have a secondary cause and to suffer end-organ damage. Most individuals with resistant hypertension will achieve normotension with conscientious treatment decisions. Patients must be approached in a stepwise manner beginning with traditional antihypertensive therapy followed gradually by additional agents to reach a quadruple or five-drug compound regimen if necessary. In those who remain hypertensive despite thorough medical management, there are interventional options currently under development which are promising but require further research.

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