Clinical Investigations from the RACP | PEER REVIEWED ARTICLE | POINTS: 2 CPD/2 PDP

Investigation of the patient with hypertension

In this series, we present authoritative advice on the investigation of a common clinical problem, specially commissioned for family doctors and written by members of the Royal Australasian College of Physicians.

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The diagnosis of hypertension should be made over several visits of the patient to the GP surgery. Use of a mercury sphygmomanometer remains the most accurate method of measuring a patient's blood pressure level. However, mercury devices are being phased out of the clinical environment, and automated blood pressure devices are now frequently used. Such devices require validation initially and every six months to ensure accuracy.

If available, 24-hour ambulatory blood pressure monitoring is useful to confirm the diagnosis of hypertension, particularly when the presence of white-coat (or office) hypertension is likely. White-coat hypertension should be suspected in a patient with:

- significant variations in blood pressure measurements between visits to the GP or between practitioner measurements
- elevated blood pressure measurements, who is otherwise fit and healthy
- resistant hypertension
- symptoms suggestive of both hypotension and hypertension.

Twenty-four-hour ambulatory blood pressure monitoring (Table 1)[1] is also useful to evaluate a patient for 'reverse white-coat hypertension', now known as masked hypertension. Masked hypertension occurs when a patient's blood pressure is higher when measured outside the doctor's office than when measured inside the office – that is, the patient has a controlled office blood pressure level but an elevated home or 24-hour blood pressure level. This condition is not yet fully understood, but is thought to represent an increased risk for cardiovascular disease.

Patients with elevated home blood pressure but controlled office blood pressure should undergo 24-hour ambulatory blood pressure monitoring. Current evidence strongly suggests that 24-hour blood pressure readings are more accurately associated with target organ damage than office blood pressure measurements.[2] This supports the use of out of office blood pressure monitoring in patients with suspected hypertension.

IN SUMMARY

- **The diagnosis of hypertension should be made over several visits of the patient to the GP surgery.**
- **Twenty-four-hour ambulatory blood pressure monitoring is useful to evaluate a patient for white-coat hypertension or masked hypertension.**
- **Home blood pressure monitoring is now frequently used by patients in the management of their condition.**
- **All patients with hypertension should be screened for diseases of the kidney, which are probably the most common secondary cause of hypertension.**
- **Other secondary causes of hypertension to consider include primary aldosteronism and phaeochromocytoma.**

Home blood pressure monitoring is now frequently used by patients in the management of their condition. Patients should be instructed on the correct method of using a home device.[3] Generally, two or three measurements should be made with the patient sitting down, and the average measurement recorded. Note that the upper limit of normal home blood pressure level is lower than that of the office levels (mean of multiple readings) at below 135/85 mmHg (Table 1). Some authors advocate ignoring the first reading. There are many blood pressure monitoring devices that have been validated as being acceptable for clinical use.[3]

End-organ damage caused by hypertension and associated clinical conditions

The presence of end-organ damage places the patient with hypertension in a higher risk category and correspondingly lowers his or her blood pressure target. It is therefore imperative to evaluate the patient for end-organ damage to stratify the patient's risk and to monitor the status of the end organs. The commonly affected organs – the heart, kidneys, vasculature and cerebrovascular system – can generally be easily assessed.

History and physical examination will identify the majority of clinical conditions associated with hypertension (Table 2). These are diseases that should be considered in any patient with hypertension with each disease managed on its merits. Generally, antihypertensive therapy should be used when one or more of these associated conditions is present, regardless of blood pressure.

All patients diagnosed with hypertension should have initial screening tests undertaken, as listed in Table 3.

Investigations for secondary hypertension

Chronic kidney disease

All patients with hypertension should be screened for diseases of the kidney, which are probably the most common secondary cause of hypertension. If a urinalysis and estimated glomerular filtration rate (eGFR) measurement are both normal, significant kidney disease can be excluded in most cases. If these measurements are abnormal, then an ultrasound or a computed tomography scan of the kidneys will give further information about renal anatomy and exclude other reversible problems. If chronic kidney disease is diagnosed, referral should be considered, according to the Kidney Health Australia guidelines.[4]

Primary aldosteronism

Primary aldosteronism is a syndrome of hypertension accompanied by salt and water retention secondary to excess levels of aldosterone. Hypokalaemia is commonly described in patients with primary aldosteronism; however, in about 50% of patients with primary aldosteronism, the serum potassium levels are normal. Potassium levels in the

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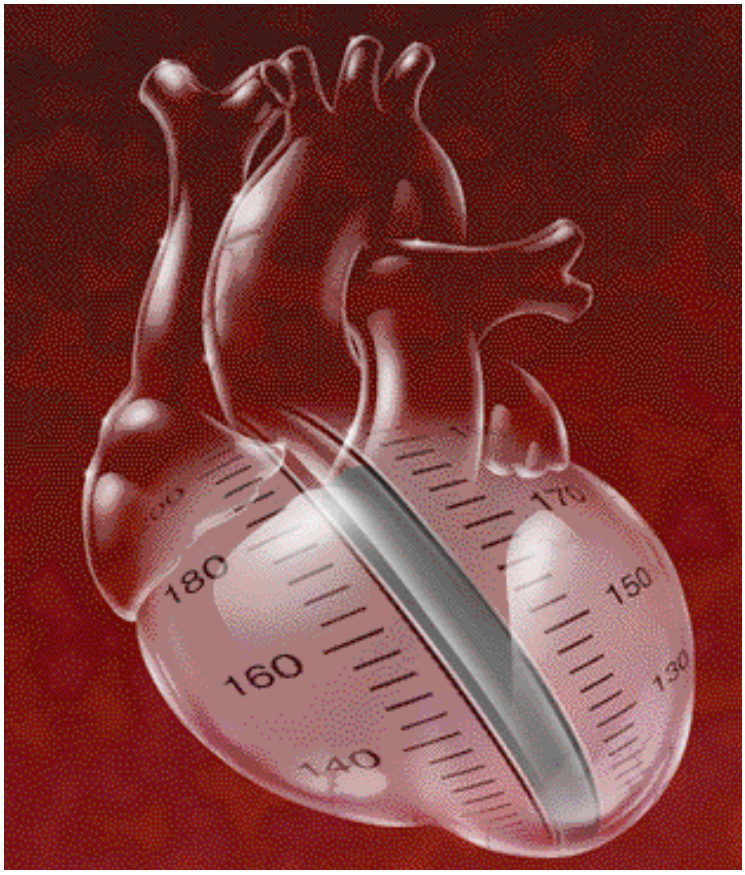

An elevated blood pressure measured during a patient's routine physical examination must be carefully considered before a diagnosis of hypertension can be made. White-coat hypertension can be a possible cause of the increase, but hypertension can be a symptom of other serious conditions.

Table 1. Normal values for office, 24-hour and home blood pressure in nonpregnant adults*[1]

Blood pressure reading	Normal value (mmHg)
Office (seated, resting)	<140/90
24-hour	
• Daytime (awake)	<135/85
• Night-time (asleep)	<120/70
• 24-hour average	<130/80
Home (awake, mean of multiple measurements)	<135/85

* 24-hour blood pressure ranges reproduced with permission from the National Heart Foundation of Australia.[1]

Table 2. Clinical conditions and end-organ disease associated with hypertension*[1]

Associated clinical conditions

Diabetes
- In either of the following:
  - adults with diabetes aged >60 years
  - adults with diabetes and microalbuminuria

Cerebrovascular disease
- Ischaemic stroke
- Transient ischaemic attack
- Cerebral haemorrhage

Coronary heart disease
- Myocardial infarction
- Angina
- Coronary revascularisation

Chronic heart failure

Chronic kidney disease
- Diabetic nephropathy
- Glomerulonephritis
- Hypertensive kidney disease

Aortic disease
- Dissecting aneurysm
- Fusiform aortic aneurysm

Peripheral arterial disease (clinical diagnosis or ankle brachial index <0.9)

Hypercholesterolaemia
- Total cholesterol >7.5 mmol/L

Family history or previous diagnosis of:
- premature cardiovascular disease or
- familial hypercholesterolaemia

End-organ disease

Left ventricular hypertrophy
- Diagnosed by electrocardiogram or echocardiogram

Microalbuminuria
- Defined as either of the following:
  - albumin/creatinine ratio ⩾2.0 mg/mmol (males) or ⩾2.5 mg/mmol (females) on a spot urine screening test
  - 24-hour urinary albumin excretion rate ⩾20 µg/min

Chronic kidney disease
- Presence of either of the following:
  - proteinuria defined as protein/creatinine ratio ⩾30 mg/mmol on a spot urine test or urine protein >300 mg/day on a timed urine sample
  - estimated glomerular filtration rate <60 mL/min/1.73 m^2

Vascular disease
- Atherosclerotic plaque (aorta, carotid, coronary, femoral and iliac arteries) evident on ultrasound or radiology
- Hypertensive retinopathy (grade II or greater)

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lower normal range and bicarbonate levels in the upper normal range in the absence of diuretic therapy are suggestive of an excessive secretion of mineralocorticoid (aldosterone).

Primary aldosteronism should be considered in patients with:
- proven resistant hypertension
- low or low-normal serum potassium
- a family history of primary aldosteronism.

The aldosterone to renin ratio is generally the most simple and sensitive test available to screen patients for primary aldosteronism. An elevated ratio is suggestive, but not diagnostic, of aldosteronism.

The aldosterone to renin ratio is influenced by some medications:
- beta blockers suppress renin production and therefore increase the aldosterone to renin ratio
- diuretics, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers stimulate renin release and therefore lower the aldosterone to renin ratio.

Measurement of the aldosterone to renin ratio should be performed after a washout period of at least one week while the patient is not taking any medications (if safe). If this is not possible or unsafe, the use of prazosin (1 to 5 mg three times a day) and/or verapamil (180 to 240 mg daily) instead of the usual agents will have minimal effect on the ratio during the seven- to 10-day period prior to the blood test.

To confirm the diagnosis of primary aldosteronism, patients with an elevated aldosterone to renin ratio should have suppression testing and, possibly, adrenal vein sampling, best undertaken in specialist units. If a patient has a family history of aldosteronism, a diagnosis of familial hyperaldosteronism type 1 (dexamethasone-suppressible aldosteronism) should be considered.

In patients for whom the series of investigations to determine primary aldosteronism is too difficult or in whom

treatment with adrenalectomy surgery would not be an option, it is quite reasonable to use a therapeutic trial of a mineralocorticoid blockade, such as spironolactone 12.5 to 25 mg daily or amiloride 5 to 10 mg twice daily. Extreme caution should be exercised when using a mineralocorticoid blockade, especially in patients with a reduced eGFR or those also taking ACE inhibitors, angiotensin receptor blockers, other diuretics or NSAIDs, because of the risk of hyperkalaemia and/or a further reduction in eGFR.

Phaeochromocytoma

Although phaeochromocytoma is a rare disease, it should be considered in patients with hypertension:

- who are younger in age (<30 years)
- who have a family history of phaeochromocytoma
- that is resistant or
- who have flushing symptoms.

The 24-hour urinary catecholamine excretion test is often used to screen patients for phaeochromocytoma. However, the fasting plasma metanephrine and normetanephrine measurement is now available. It is a simpler test, which avoids the need for urine collection, and is highly sensitive for phaeochromocytoma. A low positive result (i.e. less than three to four times the upper limit of normal) may well be a false-positive result because the test lacks specificity, but a strongly positive result (i.e. more than four times the upper limit of normal) is generally diagnostic of phaeochromocytoma.

False-positive results can be reduced by the patient fasting before the test, repeating the test (if a low positive result is given) and withdrawing drugs that lead to false-positive tests. Such agents include alpha and beta blockers, sympathomimetics and tricyclic antidepressant agents. Furthermore, 24-hour urine metanephrine excretion testing is helpful in positive cases because this test is more specific for a tumour and will exclude false positives.

Renovascular disease

In view of the possibility of fibromuscular hyperplasia of the renal artery, it is reasonable to screen for renal artery stenosis in younger (<30 years) patients with hypertension, particularly young women. Patients with fibromuscular hyperplasia generally respond well to endovascular revascularisation, with approximately 80% of patients having their hypertension significantly improved or completely resolved after the procedure.[5] The gold standard test for renovascular disease is the digital subtraction angiogram and should be performed when there is a high index of suspicion for the condition. Other useful screening tests include the computed tomography renal angiogram and MRI of the kidneys. The Doppler ultrasound is a less useful screening test.

Atherosclerotic renal artery stenosis is now managed less aggressively. A series of studies has been published and presented that does not demonstrate convincing evidence of benefit of treatment for either progression of chronic kidney disease or control of hypertension. Therefore, it is reasonable in older patients (i.e. those with risk factors for atherosclerosis) not to screen for renal artery stenosis or revascularise if blood pressure is controlled and kidney function is stable. (See cari.org.au for the 2009 Caring for Australasians with Renal Impairment Guidelines on Renovascular Disease; currently under development.)[6]

Other causes of hypertension

Other causes of hypertension are rare. Generally patients who have been fully investigated and still have uncontrolled hypertension should be referred to a specialist.

Current targets for hypertension control

In the *Guide to Management of Hypertension 2008*, blood pressure targets have been simplified (Table 4).[1] Note that 'lower if tolerated' is emphasised, reflecting the growing body of evidence that lowering blood pressure beyond the target is beneficial, rather than harmful.

Achieving blood pressure targets is difficult. Even in clinical trials or trials of different drugs in patients with hypertension, blood pressure targets are only met in 50 to 80% of such patients. Although there are medical reasons for this suboptimal rate, one of the major causes is a reluctance of the doctor to change medication at patient visits, even if the target has not been met. It is important that this is recognised as a barrier to effective treatment in the absence of other causes of treatment failure, such as nonadherence with therapy, symptoms or other patient-related factors.

Management of hypertension uncontrolled by medications

Resistant or nonresponsive hypertension is diagnosed when a patient has not

Table 3. Initial investigations in patients with hypertension*[1]

- Dipstick test for haematuria (plus urine microscopy if positive)
- Dipstick test for proteinuria (plus 24-hour urinary protein excretion measurement if positive)
- Dipstick test or measurement of albumin to creatinine ratio for microalbuminuria (plus 24-hour urine collection if positive)
- Blood analysis for levels of sodium, potassium, chloride, bicarbonate, urea, creatinine, uric acid, haemoglobin, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides and liver enzymes
- Electrocardiogram for coronary artery disease, arrhythmia or left ventricular hypertrophy

* Adapted with permission from the National Heart Foundation of Australia.[1]

continued

Table 4. Blood pressure treatment targets in adults*[1]

Patient group	Target (mmHg)
People with proteinuria >1 g/day (with or without diabetes)	<125/75
People with the following associated clinical condition(s) or end-organ damage: • coronary heart disease • diabetes • chronic kidney disease • proteinuria (>300 mg/day) • stroke/transient ischaemic attack	<130/80
People with none of the above conditions	<140/90 or lower if tolerated

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responded to the maximum dose of at least two agents prescribed to control hypertension. Twenty-four-hour ambulatory blood pressure monitoring is useful in this circumstance as the gold standard noninvasive measurement of blood pressure in a patient undergoing either nonpharmacological or pharmacological treatment of hypertension. About 30% of patients with resistant office hypertension despite therapy may have controlled hypertension when assessed by 24-hour ambulatory blood pressure monitoring.[7] If ambulatory blood pressure monitoring is not available, home blood pressure monitoring can be used.

Nonadherence or poor compliance with medication and white-coat hypertension can generally be assessed by 24-hour blood pressure monitoring. Asking the patient to document physical activity and timing of medication administration will usually allow an assessment of adherence to be made.

Sleep apnoea should be considered in the patient who is overweight or snores heavily. The patient should be asked what other drugs he or she is taking because of the possibility that other drugs may raise blood pressure levels. Finally, a high salt intake is increasingly recognised as contributing to resistant hypertension, particularly in patients receiving ACE inhibitor-based treatment, who are not taking a diuretic or are fluid overloaded.

Investigation or referral is appropriate in the patient with nonresponsive hypertension proven by 24-hour ambulatory blood pressure monitoring. It is reasonable to use a combination of an ACE inhibitor or angiotensin receptor blocker, with a calcium channel blocker and/or a diuretic in such patients. Other useful agents to trial include prazosin, spironolactone, beta blockers and frusemide (especially when there is fluid retention); however, care must be taken because of interactions and side effects when multiple agents are used.

Conclusion

The investigation of patients with hypertension is now directed towards assessment of end-organ damage, associated clinical conditions and secondary causes. The importance of correct blood pressure measurement both in the GP surgery and outside it is now better understood and forms a major part of the assessment and ongoing management of the patient with hypertension. MT

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COMPETING INTERESTS: None