HYPERTENSION

CHAPTER 8

IN THIS CHAPTER

CARDIOVASCULAR PHYSIOLOGY

CLINICAL BIOCHEMISTRY OF HYPERTENSION

High blood pressure, or hypertension, is one of the key risk factors for cardiovascular disease. It is of huge public health significance, both in terms of its consequences and its treatment, with as many as 75 million adults having hypertension in the USA alone. In only a small minority of cases is the underlying cause understood: on a population basis, nearly all hypertension is labeled as essential, a euphemism for cause unknown. The physiology of blood pressure control is well understood, however, and many types of drug have been developed which target specific control mechanisms, with more drugs under development. It is important for the individual patient concerned not to miss the small minority of cases that do have a well-characterized cause in order to ensure that they receive the correct treatment.

8.1 CARDIOVASCULAR PHYSIOLOGY

Blood pressure

The blood in the cardiovascular system is pumped around the body in a series of closed vessels. As the left ventricle contracts (systole) and relaxes (diastole), the pressure that is exerted upon the walls of the arteries varies, normally rising to around 120 mmHg during systole and falling to around 80 mmHg during diastole (**Figure 8.1a**). Arterial blood pressure is therefore always quoted as two figures, such as 120/80 mmHg, where the first figure is the systolic blood pressure (SBP) and the second figure is the diastolic blood pressure (DBP). Such large variations in blood pressure over the cardiac cycle are only apparent in the arteries; by the time blood is flowing into the smallest arterioles and the capillaries, the blood pressure profile is smooth (**Figure 8.1b**). Tissue perfusion pressure is determined by the mean arterial blood pressure (MABP), which can be estimated using a simple equation:

$$\mathbf{MABP = DBP + [(SBP - DBP)/3]}$$

Inserting the normal blood pressure figures from above (120/80 mmHg), MABP is 93 mmHg. Mean arterial blood pressure is not simply the arithmetic mean of SBP and DBP since, at rest, the left ventricle spends twice as much time in diastole as it does in systole. Thus, DBP makes a greater contribution to

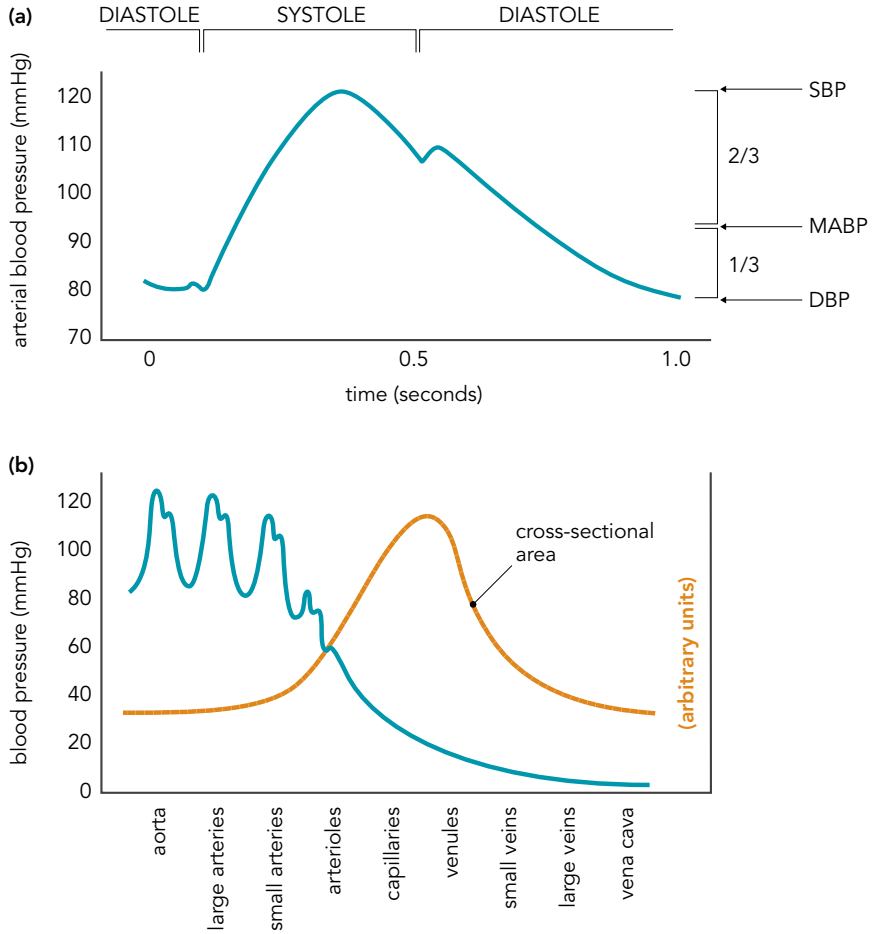

Figure 8.1 Blood pressure profiles. (a) Aortic pressure plotted against time and showing the cardiac cycle. (b) Pressure and cross-sectional area throughout the systemic circulation. Note that systolic and diastolic variations in pressure are seen only on the arterial side of the vascular system (left side of graph). The total cross-sectional area of the vascular tree increases as the diameter of the individual vessels decreases, reaching a maximum in the capillaries. MABP, mean arterial blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

MABP (see Figure 8.1a). The figure for MABP is the point on the blood pressure curve that, if one were to draw a horizontal line across the curve, would give two equal areas above and below that line.

The two important determinants of MABP are cardiac output (CO) and total peripheral resistance (TPR), and increases in either or both tend to increase MABP. CO is the arithmetic product of heart rate and stroke volume (the volume of blood ejected from the left ventricle during each heart beat). Thus, changes in heart rate, stroke volume, or circulating blood volume have the potential to alter MABP.

MABP increases with increasing TPR. The factors affecting resistance to flow (R) can be described by the following equation:

$$R = 8\eta L/\pi r^4$$

where η is blood viscosity, L is length of blood vessel, and r is blood vessel radius.

Under normal second-by-second circumstances in a given vascular bed, η and L do not change, but r can be influenced markedly by changing the degree of constriction of the smooth muscle in the wall of the blood vessel. For example, a reduction in r of only 10% results in a 52% increase in R, while reducing r by 20% increases R by 144%. Hence, vessel radius (and the degree of constriction of smooth muscle in the walls of blood vessels) has the largest effect on TPR. This is one of the methods that the body uses to alter MABP; generalized vasoconstriction can increase TPR and thereby raise MABP. Capillaries make the greatest contribution to the total cross-sectional area of the cardiovascular system (see Figure 8.1B) and while it might be thought that capillary constriction

or dilatation might be important in altering TPR, capillary walls per se have no smooth muscle and thus little can be done to alter their cross-sectional area. However, flow to the capillary beds is controlled by the arterioles that feed them, and the walls of these arterioles are very muscular such that constriction or dilatation of these vessels results in large changes in TPR. For this reason, arterioles are commonly known as the resistance vessels of the cardiovascular system and are thought to make the greatest contribution to variations in TPR.

Neural mechanisms for control of blood pressure

Blood pressure is monitored by baroreceptors in the walls of blood vessels in various parts of the body. One of the major baroreceptor sites is in the carotid body, where distension of the wall of the carotid artery results in increased stimulation of specialized nerve endings and increased firing of those neurons. Other baroreceptors exist in the arch of the aorta. These baroreceptors send processes via the glossopharyngeal nerve (in the case of the carotid baroreceptors) and the vagus nerve (in the case of the aortic baroreceptors) to cardiovascular monitoring centers in the brain stem. Here, the neurons synapse with other neurons that control the firing rate of parasympathetic (vagal) and sympathetic (cardiac accelerator) nerve fibers to the heart, and sympathetic nerve fibers (vasomotor nerves) to the vasculature. In general, activation of baroreceptors by increased MABP leads to reduced sympathetic outflow from the cardiovascular center and increased vagal outflow to the heart. A reduction in sympathetic outflow by this mechanism would reduce heart rate and stroke volume and decrease vasomotor tone, thereby reducing CO, TPR, and MABP. An increase in parasympathetic outflow would reduce heart rate, thereby reducing CO and MABP. This negative-feedback loop functions to maintain MABP within relatively tight limits. One problem with baroreceptor control of blood pressure is that such receptors, if exposed to high levels of MABP for significant periods of time (1–2 days), reset their basal firing rate to suit the new levels of basal MABP. This can mean that sustained increases in MABP (as in hypertension) cannot be compensated for by normal mechanisms.

Endocrine mechanisms for control of blood pressure

Baroreceptor mechanisms in the body also serve to maintain blood pressure over the medium to long term. Such mechanisms are generally hormonal in nature and are therefore less rapid than the neural pathways described above. In view of the diverse nature of the potential hormonal responses to a change in blood pressure over the medium to long term, it would be simplistic to state that the consequences of a particular alteration in blood pressure would have a predictable effect on the blood concentration of a given set of circulating hormones. However, it is important to be able to predict what effect the various hormones individually might have on different parameters that have a role to play in determining blood pressure.

In general, the four major hormone systems that are at play are adrenal medullary norepinephrine/epinephrine, the renin–angiotensin–aldosterone system, adrenal cortical cortisol, and vasopressin (see **Table 8.1** for a summary of their actions).

The catecholamine hormone epinephrine is released from the adrenal medulla in response to a fall in MABP, as part of the sympathetic response. The adrenal medulla is a collection of innervated nerve cell bodies (chromaffin cells) which have not developed axonal processes but which normally discharge their transmitter (80% epinephrine, 20% norepinephrine) into the bloodstream. Thus, medullary epinephrine and norepinephrine are hormones but are released on activation of the sympathetic branch of the autonomic nervous system. These hormones act on α- and β-adrenoceptors on a wide range of body tissues to exert a physiological effect; in the case of the heart and blood vessels, they stimulate cardiac β-adrenoceptors and vascular α-adrenoceptors (which cause

TABLE 8.1 Major hormones affecting function of the cardiovascular system

Hormone	Specific effect	Effect on blood pressure
(Nor)epinephrine	Peripheral vasoconstriction	Increased MABP, through increased TPR and increased CO
	Increased heart rate and force	
Angiotensin II	Peripheral vasoconstriction	Increased MABP, through increased TPR and increased CO
	Aldosterone secretion	
	Vasopressin secretion	
	Thirst	
Aldosterone	Increased salt and water reabsorption	Increased MABP, through increased CO
Cortisol	Permissive role—maintains/increases expression of adrenoceptors on peripheral tissues	Helps maintain or increase MABP
Vasopressin	Increased water reabsorption	Increased MABP, through increased CO and increased TPR
	Vasoconstriction	

CO, cardiac output; MABP, mean arterial blood pressure; TPR, total peripheral resistance.

vasoconstriction) to raise CO and TPR, respectively. This is also part of the general "fight or flight" response to a threatening stimulus. In conditions such as pheochromocytoma (where tumors develop from chromaffin cells), high circulating levels of these hormones can result in hypertension and a range of other effects.

The synthesis of epinephrine from norepinephrine in the adrenal medulla is influenced by cortisol, released from the adrenal cortex; exposure of chromaffin cells to cortisol results in the induction of the enzyme phenylethanolamine-*N*-methyl transferase (PNMT), which converts norepinephrine to epinephrine. Cortisol also maintains expression of adrenoceptors on the various target cells of the sympathetic nervous system such as the heart and blood vessels. Thus, when circulating levels of cortisol are abnormally low or high, this can result in low or high blood pressure, respectively.

The renin–angiotensin–aldosterone system is complex (**Figure 8.2**). Renin (released from the juxtaglomerular cells of the afferent arteriole of the renal

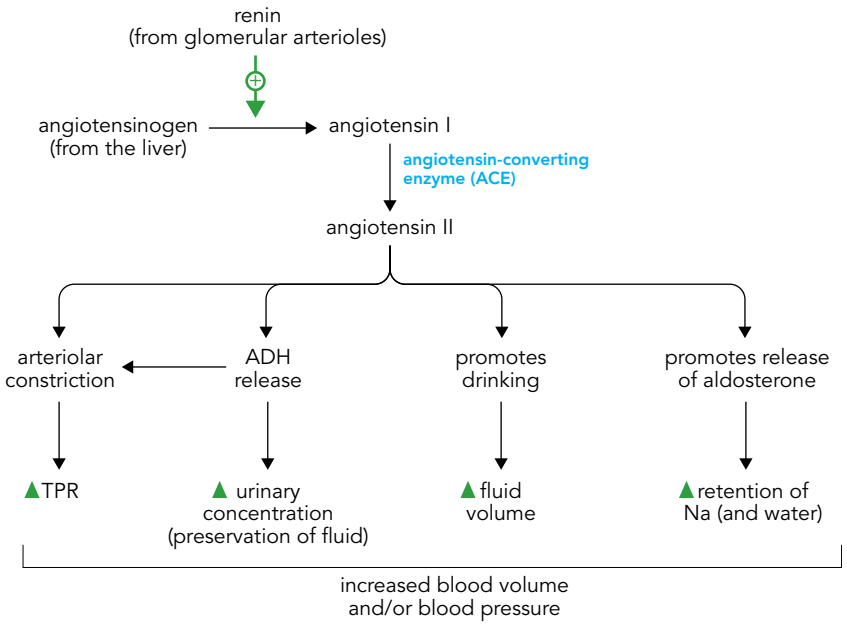

Figure 8.2 The role of the renin–angiotensin–aldosterone system in fluid balance and long-term regulation of blood pressure. Angiotensin II has multiple effects, the most important of which are release of aldosterone from the adrenal cortex and arteriolar constriction. ADH, antidiuretic hormone (vasopressin); TPR, total peripheral resistance.

corpuscle in response to a reduction in perfusion; see Chapter 4) circulates in the blood and converts angiotensinogen (a peptide produced by the liver) to angiotensin I. Angiotensin I is, in turn, converted to angiotensin II by the action of angiotensin-converting enzyme (ACE), which is present on vascular endothelial cells.

In situations where blood pressure is normal but there is significant renovascular disease (for example, renal artery stenosis), the resultant underperfusion of the kidney can result in renin release and trigger a cascade of events leading to elevated blood pressure. Diseases of the adrenal cortex, resulting in the under- or overproduction of adrenal cortical hormones such as aldosterone, can also have marked effects on fluid balance and blood pressure.

8.2 CLINICAL BIOCHEMISTRY OF HYPERTENSION

Elevated blood pressure is an important risk factor for cardiovascular disease, especially ischemic heart disease and stroke. Stroke may be due to either atherosclerotic disease or hemorrhage. Hypertension is involved in the pathogenesis of both types, as it is a risk factor for atheroma and increases the mechanical stress in areas of weakened arterial wall within the cerebral circulation. In common with other risk factors, such as blood lipids, blood pressure level is normally distributed within the population, with no threshold below which cardiovascular events never occur. Hence, the definition of hypertension is arbitrary but based on the observed risk of events in the population, particularly strokes. A 2 mmHg increase in average systolic blood pressure is associated with a 7% increase in death from heart disease and 10% from stroke. These are increments in relative risk, but modern cardiovascular risk assessment places much more emphasis on an individual's absolute risk, which is determined by all of their risk factors. This is expressed as a risk of that individual suffering a major cardiovascular event, such as a heart attack, in the next 10 years, and theoretically can be anywhere between 0 and 100%. The definition of high risk is arbitrary and varies over time, according to expert opinion in balancing the risks (and financial costs) against the benefits of treatment. The threshold has been lowered from 30% to 10% within the last two decades and may be reduced even further. Assessment of absolute risk can be done using charts or online calculators, which require input of factors such as age, gender, blood pressure, cholesterol, and smoking status. Definitions of hypertension and thresholds for treatment undergo periodic re-evaluation by expert panels as new evidence emerges. Currently, different stages of hypertension are recognized. Stage 1 is defined as office or clinic blood pressure (BP) of 140/90 mmHg or ambulatory BP of 135/85 mmHg. Stage 2 is 160/100 mmHg or 150/95 mmHg. Severe hypertension is BP 180/110 mmHg or above. The stage is determined by the highest BP; that is, the SBP or DBP.

Clinical practice point 8.1

The threshold blood pressure for the definition of hypertension is arbitrary.

Clinical practice point 8.2

An individual's absolute risk of cardiovascular events depends on all their risk factors.

Biochemical investigations are used to:

- Investigate the cause
- Monitor the effects of the disease and its treatment
- Assess other cardiovascular risk factors

The vast majority of hypertension is termed essential because its cause is not well understood. The pathogenesis appears to be a complex interplay of multiple genes involved in the regulation of neural and endocrine control of blood pressure, along with environmental factors such as salt and alcohol intake, obesity, and stress.

Clinical practice point 8.3

Most hypertension is essential: its cause is unknown.

A small proportion of hypertensive patients (around 5–10%) have an underlying disorder that raises blood pressure (termed secondary hypertension). This proportion is higher amongst patients who are younger, or who are resistant to treatment with standard drugs, or who have additional symptoms. All of these factors are indications to investigate further.

Clinical practice point 8.4

Secondary hypertension should be considered in young people, in resistance to drug therapy, and if additional symptoms or signs are present.

Pheochromocytoma

Pheochromocytoma is a tumor of catecholamine-secreting tissue in the sympathetic nervous system. Classically they arise from cells within the adrenal medulla, but extra-adrenal tumors make up about 10% of cases and may occur anywhere along the sympathetic chain. According to the 2004 World Health Organization classification, such tumors should be termed paraganglionomas rather than pheochromocytomas. Most commonly these tumors secrete norepinephrine, but epinephrine or very rarely dopamine may be the predominant hormone. Secretion is episodic and blood pressure may vary throughout the day, although sustained hypertension also occurs. Other symptoms associated with catecholamine release include palpitations, headache, pallor, abdominal pain, and severe anxiety attacks.

The majority of pheochromocytomas are benign in the sense that the cells do not metastasize but are not clinically benign in terms of their endocrine effects, which may eventually be fatal due to causing a hypertensive crisis. Around 10% are malignant tumors and a similar number are bilateral.

Biochemical tests to diagnose pheochromocytoma are based on the measurement of catecholamines or their metabolic products (metanephrines) and may be performed on urine or plasma. There are advantages and disadvantages to each of these.

Measurement of fractionated urinary catecholamines (epinephrine and norepinephrine) has been the most widely used test for the last two decades, having superseded the assay for vanillylmandelic acid (VMA), an end-stage metabolite of catecholamines. Measuring VMA is much less sensitive for detecting pheochromocytoma and is also prone to interference from foodstuffs and prescribed and over-the-counter medicines. The assay of catecholamines is relatively straightforward to perform and samples are stable as long as they are kept at acid pH. The 24-hour urine collection period allows an integrated measurement, which avoids the problem of intermittent secretion being missed. Plasma catecholamines can also be measured, but these are very unstable and the low concentrations are technically demanding to assay. Few laboratories therefore offer this test.

Recent studies have cast some doubt on the theoretical basis of using catecholamines to detect pheochromocytoma. This is because catecholamines may be metabolized to metanephrines (metanephrine and normetanephrine) within the tumor itself (**Figure 8.3**). Thus secretion of catecholamines into the blood, and ultimately the urine, will be lower than predicted. However, the diagnostic value of plasma or urine metanephrines will be higher. This has been confirmed in studies indicating that metanephrines have sensitivities of 97–99% compared to 85–90% for catecholamines.

Sensitivity is the most important attribute for detecting a rare and potentially fatal tumor, but a high degree of specificity is also required to avoid false positive results requiring further testing. The degree of elevation above the

Analytical practice point 8.1

24-hour urine metanephrines and catecholamines are the tests of choice for diagnosis of pheochromocytoma.

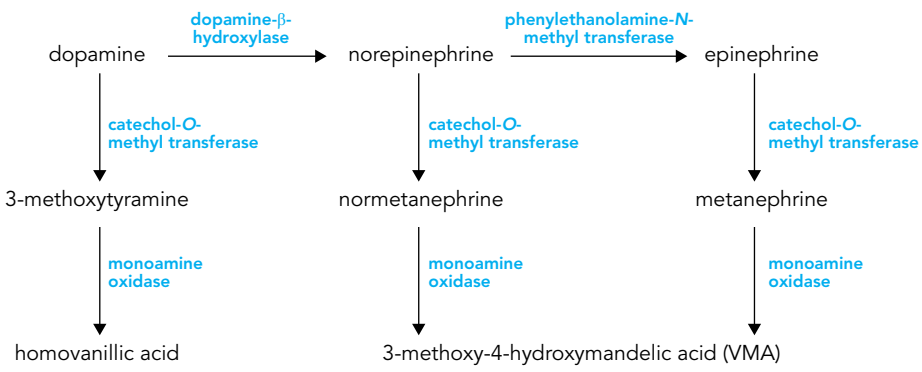

Figure 8.3 Metabolic steps in the interconversion of the catecholamines and breakdown of the catecholamines to their major metabolites.
The three vasoactive hormones of the adrenal medulla—dopamine, norepinephrine, and epinephrine—are each converted by catechol-*O*-methyl transferase to metanephrines and then by monoamine oxidase to the end products homovanillic acid and 3-methoxy-4-hydroxymandelic acid (vanillylmandelic acid; VMA). All are excreted into the urine in increased amounts in the presence of a pheochromocytoma, an autonomously secreting tumor of the adrenal medulla.

reference range is important in determining the probability of a tumor, since minor rises are often seen with some drugs, including those used for treating hypertension. It is also recognized that hypertension itself is associated with modest increases in catecholamine secretion. It is therefore preferable to use a reference range that has been derived from a hypertensive population rather than a normotensive one.

Plasma metanephrines have a slightly higher sensitivity than 24-hour urine metanephrines and avoid the inherent difficulties in making a complete collection. They are, however, technically more difficult to measure at concentrations of less than 1 nmol/L, compared to levels of around 1 μmol/L in urine.

To improve the diagnostic value of plasma metanephrines, they may be measured before and after the administration of clonidine. In normal individuals, clonidine suppresses catecholamine secretion, but this does not occur in pheochromocytoma patients. An additional test that may help to confirm the presence of a pheochromocytoma is chromogranin A. This is a protein released from the vesicles containing catecholamines and levels are increased in pheochromocytoma, as well as in a number of other conditions where secretion from neuroendocrine cells is increased, for example carcinoid syndrome.

In a small number of pheochromocytomas, dopamine is co-secreted, and in an even smaller proportion of cases, dopamine alone is produced. These dopamine-only tumors do not cause hypertension or other specific clinical effects and so present late, once they have enlarged or spread. For this reason, dopamine-secreting tumors are believed to be more likely to be malignant. However, this is probably not an intrinsic biological property, just a reflection of late presentation. Dopamine is measured on the same chromatogram as epinephrine and norepinephrine when high performance liquid chromatography is used to measure urine catecholamines. Most high dopamine results are due to renal secretion, which increases in natriuresis. Occasionally, very high dopamine excretion is seen but this is more likely to be due to the therapeutic use of levodopa to treat Parkinson's disease rather than dopamine-secreting pheochromocytoma.

Primary hyperaldosteronism

Some aspects of hyperaldosteronism are discussed in Chapter 11. The underlying pathology may be an aldosterone-secreting tumor (usually benign [Conn's syndrome]), hyperplasia of the zona glomerulosa, or an interesting variant called glucocorticoid-suppressible hyperaldosteronism. This variant is due to a dominantly inherited hybrid gene which encodes an enzyme with properties of both 11β-hydroxylase and aldosterone synthase. This results in adrenocorticotropic hormone (ACTH)-dependent production of aldosterone in the zona fasciculata, which can be inhibited by giving glucocorticoids to suppress ACTH secretion by the anterior pituitary.

Primary hyperaldosteronism is suspected in patients with refractory hypertension, particularly when hypokalemia is present or easily provoked by low doses of thiazide diuretics. However, it is important to recognize that up to 40% of primary hyperaldosteronism cases may be associated with normokalemia. The prevalence of Conn's syndrome is often said to be up to 5% in hypertensive patients, but this is likely to be an overestimate due to selection bias. The initial investigation of suspected primary hyperaldosteronism is measurement of simultaneous renin and aldosterone, with the results expressed as a ratio. Classically, the aldosterone will be raised and the renin suppressed, giving a high ratio. Unfortunately, a number of drugs commonly used to treat hypertension interfere with the renin–angiotensin–aldosterone axis and may give rise to spuriously high or low ratios. If possible, patients should be taken off these drugs and managed with α-adrenoceptor antagonists (α-blockers), which have the least effect. This is often difficult to achieve, as the very reason for investigation is that blood pressure is poorly controlled, and clinicians may be unhappy to accept suboptimal treatment.

Analytical practice point 8.2

Aldosterone–renin ratio is the first-line test for primary hyperaldosteronism, but can be affected by antihypertensive drugs.

If a high aldosterone–renin ratio is found it requires further investigation, as it is not in itself diagnostic. Theoretically, adenomas are not sensitive to angiotensin II (release provoked by a change of posture to standing) but are sensitive to ACTH (which has diurnal variation), whilst the opposite is the case for hyperplasia. Unfortunately, postural tests to distinguish adenomas from hyperplasia are not reliable. Adrenal imaging has the disadvantage of detecting a high number of nonfunctioning adenomas, which are present incidentally (so-called incidentalomas). Sometimes, selective venous sampling from catheterization of the adrenal veins is required to determine if one side is secreting significantly more aldosterone than the other.

CASE 8.1

A 35-year-old man is found to have stage 2 hypertension (blood pressure 163/92 mmHg) at a routine health check. He is not overweight and does not drink alcohol. His BP does not improve with salt restriction and he is started on a thiazide. This does not improve his BP either and his plasma potassium is found to be low (2.9 mmol/L [2.9 mEq/L]). He is referred to a hospital hypertension clinic.

	SI units	Reference range	Conventional units	Reference range
Plasma				
Renin (activity)	0.1 pmol/L/h	1.1–2.7	0.05 ng/mL/h	0.6–4.3
Aldosterone	450 pmol/L	55–250	16 ng/dL	2–9
Aldosterone–renin ratio	4500	0–900	320	0–20

- What is the significance of the hypokalemia and lack of response to treatment?
- What do the renin and aldosterone results indicate?

A mass is seen in the right adrenal gland on computed tomography scanning. He undergoes selective venous sampling using cannulas placed in the adrenal veins.

	SI units	Reference range	Conventional units	Reference range
Aldosterone				
Right arm	450 pmol/L	55–250	16 ng/dL	2–9
Right adrenal vein	1200 pmol/L	55–250	43 ng/dL	2–9
Left adrenal vein	220 pmol/L	55–250	8 ng/dL	2–9

- Why is aldosterone measured at three sites?
- What do the results indicate?

Hypertension in a relatively young and fit individual raises the possibility of an underlying cause; that is, secondary hypertension. This is more likely when there is little response to treatment, especially if two or more drugs are required. Hypokalemia in the presence of hypertension suggests primary hyperaldosteronism and this is confirmed by suppressed renin, high aldosterone, and raised aldosterone–renin ratio.

The presence of an adrenal mass does not prove that this is the cause of the high aldosterone because incidental tumors are common. Selective venous sampling shows the right adrenal is the source of aldosterone, thus confirming the tumor is responsible. The left adrenal secretion is suppressed, due to low renin. The result from the right arm reflects dilution of aldosterone in the total blood volume.

The role of aldosterone in essential hypertension is a subject of significant interest and debate. Although classical primary hyperaldosteronism is relatively uncommon, a significant proportion of hypertensive patients respond to the aldosterone antagonist spironolactone. There is also growing evidence that aldosterone is directly toxic to the heart, kidneys, and blood vessels and contributes to the risk of cardiovascular disease. Spironolactone is a nonselective aldosterone antagonist with a number of side effects which limit its use, and more selective drugs are under development.

Other causes of hypertension

Hypertension may be a consequence of other diseases, although it may not be the most prominent feature. Of particular importance is kidney disease, where high blood pressure may be both a cause and a consequence of decreased renal function. Blood pressure control is an important aspect of slowing the progression of chronic kidney disease. Renal function can be monitored by both plasma markers (creatinine and estimated glomerular filtration rate, eGFR) and urine markers (protein–creatinine or albumin–creatinine ratio).

Endocrine disorders causing hypertension include Cushing's syndrome, thyroid disease, hyperparathyroidism, and acromegaly. Investigations for these conditions would usually only be considered if other clinical features were apparent, however. The probability of diagnosing one of these conditions in the presence of hypertension alone would be low.

Clinical practice point 8.5

Hypertension is both a cause and a consequence of chronic kidney disease.

Biochemical monitoring of the hypertensive patient

Monitoring of the effects of blood pressure on target organs and of drug treatment, together with assessment of other cardiovascular risk factors (particularly lipids), make up the majority of biochemical testing in hypertension. Mild to moderate hypertension may respond to lifestyle measures (weight loss, aerobic exercise, and restriction of dietary salt and alcohol), but in most cases drug therapy is also required. The large number of drug classes and mechanisms of action indicates the difficulty in treating hypertension adequately. Drug classes commonly used to treat high blood pressure are listed in **Table 8.2**.

Thiazides are currently considered to be the first-line treatment, with other drugs such as ACE inhibitors, angiotensin receptor blockers (ARBs), or calcium channel antagonists being used as alternatives if additional medical conditions are present. Second-line agents include aldosterone antagonists, such as spironolactone, and α-adrenoceptor antagonists. Two, three, or even four different agents may be needed to control hypertension adequately to the target blood pressure levels recommended by expert societies around the world.

TABLE 8.2 Drugs used to treat hypertension

Drug class	Example
Thiazide	Hydrochlorothiazide
Angiotensin-converting enzyme (ACE) inhibitor	Ramipril
Angiotensin II receptor blocker	Losartan
Calcium channel blocker	Amlodipine
β-Adrenoceptor antagonist (β-blocker)	Atenolol
Loop diuretic	Furosemide
Aldosterone antagonist	Spironolactone
α-Adrenoceptor antagonist (α-blocker)	Doxazosin
Vasodilator	Hydralazine

Depending on the doses and combinations, there may be metabolic side effects, which can be detected by routine monitoring of renal function (plasma creatinine and eGFR), electrolyte levels, and uric acid.

Thiazides are diuretics at high doses and can cause a number of metabolic side effects including hyponatremia, hypokalemia, hyperglycemia, and hyperuricemia leading to gout. However, these are rarely seen in current practice as the doses used are much lower than in previous decades. There is no additional antihypertensive effect from using higher doses. Hypokalemia occurring on low-dose thiazide raises the possibility of Conn's syndrome.

Drugs that block the renin–angiotensin–aldosterone system have a predictable effect on plasma potassium: they tend to raise it. In some patients this elevation may be sufficiently high that these drugs cannot be used at all. Another risk is worsening renal impairment due to decreased blood flow to the kidneys. This may occur when the renal artery is partially obstructed, perhaps by atheroma, and the hypoperfusion stimulates the release of renin, leading to increased angiotensin II and ultimately aldosterone. Renal perfusion is therefore maintained due to the high angiotensin II levels. When an ACE inhibitor or ARB is given, the angiotensin II level cannot be maintained and the kidney is hypoperfused once again. The result of this is a rise in plasma creatinine and a fall in eGFR. Thus renal function is carefully monitored after starting ACE inhibitors or ARBs and after dose increments. The risk is especially high in patients with peripheral vascular disease as this implies atheroma is also present in the renal arteries.

Hypertension as a cardiovascular risk factor

Hypertension is not a disease per se unless the blood pressure is particularly high (>180/120 mmHg) or enters an accelerated phase with end-organ damage (so-called malignant hypertension), when it becomes a medical emergency. In the vast majority of individuals labeled as hypertensive, the blood pressure is a risk factor for future cardiovascular events, such as myocardial infarction, heart failure, stroke, or kidney failure. However, elevated blood pressure is just one of a number of risk factors—albeit an important and treatable one—which include age, gender, smoking, diabetes, and plasma lipids. All of these should be assessed in a hypertensive patient, as multiple risk factor intervention is more effective for preventing cardiovascular events than treating just one factor. Plasma lipids should be measured as part of routine cardiovascular risk assessment. Increasingly, statin drugs (HMG-CoA reductase inhibitors) are given to individuals at high cardiovascular risk (for example, 20% risk of suffering a major cardiovascular event over 10 years), including those with hypertension, irrespective of the plasma cholesterol, because of the importance of reducing multiple risk factors.