

# Hypertension: pathophysiology and treatment

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Arterial hypertension is a major cause of morbidity and mortality because of its association with coronary heart disease, cerebrovascular disease and renal disease. The extent of target organ involvement (i.e. heart, brain and kidneys) determines outcome. North American studies have shown that hypertension is a major contributor to 500 000 strokes (250 000 deaths) and 1 000 000 myocardial infarctions (500 000 deaths) per annum.

National surveys continue to reveal that hypertension is often not detected and, where diagnosed, is often inadequately treated. Among hypertensive patients, only 25% appear to be well controlled. This is particularly true of isolated systolic hypertension. Yet the prevalence of isolated systolic hypertension increases with age. Indeed, the proportion of subjects suffering from isolated systolic hypertension, as opposed to systolic and diastolic hypertension, increases from 20% in the under 40 yr to 80% in the 60–69 yr old, and to 95% in those >80 yr. There is increasing emphasis on the risk associated with systolic hypertension as the level of systolic pressure is a good predictor of coronary and cerebrovascular risk, especially in the elderly. Treatment of systolic hypertension with its wide pulse pressure is effective in terms of control of blood pressure and reduced morbidity, especially in older patients with high risk profile.

Over the past decade the management of hypertension has changed with the recognition that there is no threshold below which elevated blood pressure causes no threat to health. Recent guidelines, including those of the British Hypertension Society, make it clear that treatment of isolated systolic hypertension is as important as that of systolic and diastolic hypertension. The threshold above which hypertension should be treated to prevent long-term complications is now 140/90 mm Hg. Indeed, in Stage 1 hypertension, treatment of isolated systolic hypertension (systolic 140–159 mm Hg, diastolic <90 mm Hg), reduces the prevalence of left ventricular hypertrophy, a predictor of future morbidity and mortality. There is also a 42% reduction of the

risk of stroke and a reduction in the risk of dementia.

The hypertension optimal treatment (HOT) study indicates that the treatment goal is to reduce blood pressure to 140/85 mm Hg. It is also established that high normal blood pressure (130–139/85–89 mm Hg) progresses to Stage 1 hypertension (>140/>90 mm Hg) in >37% of individuals <64 yr and >49% of those >65 yr.

The British National Formulary recommends the following approach:

- blood pressure >220/>120 mm Hg:  
immediate therapy;
- blood pressure 200–219/110–119 mm Hg:  
confirm over 1–2 weeks, then treat; or
- blood pressure 160–199/100–109 mm Hg  
confirm over 3–4 weeks, then treat.

In patients with high blood pressure, the cumulative incidence of first cardiovascular events over 10 yr is 10% in males and 4.4% in females. Even high normal blood pressure is correlated with an increased risk of death attributable to coronary or cerebrovascular events. Whether treatment of high-normal blood pressure would prevent cardiovascular events is unknown.

## Regulation of blood pressure

The control of blood pressure is complex and will be reviewed only briefly.

### Neurogenic control

The vasomotor centre includes the nucleus tractus solitarius in the dorsal medulla (baroreceptors integration), the rostral part of the ventral medulla (pressor region), and other centres in the pons and midbrain. The arterial baroreceptors respond to vessel wall distension by increasing the afferent impulse activity. This in turn decreases the efferent sympathetic activity and augments vagal tone. The net effect is bradycardia and vasodilatation.

### Renin-angiotensin system

The protease renin cleaves angiotensin I the inactive peptide angiotensin I

### Key points

Hypertension is a cause of morbidity and mortality.

In general practice, the level of blood pressure above which treatment of hypertension is indicated is now set at 140/90 mm Hg.

Increased systemic vascular resistance, increased vascular stiffness, and increased vascular responsiveness to stimuli are central to the pathophysiology of hypertension.

Morbidity and mortality attributable to hypertension result from target organ involvement.

Newer antihypertensive agents such as ACE inhibitors and angiotensin II receptor antagonists are effective, but not more than diuretics and  $\beta$ -blockers.

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converted into an active octapeptide, angiotensin II by the angiotensin-converting enzyme (ACE). Though the renin-angiotensin system is widespread in the body, the main source of renin is the juxtaglomerular apparatus of the kidney. This apparatus senses the renal perfusion pressure and the sodium concentration in the distal tubular fluid. In addition, renin release is stimulated by  $\beta$ - and decreased by  $\alpha$ -adrenoceptor stimulation. High angiotensin II concentrations suppress renin secretion via a negative feedback loop. Angiotensin II acts on specific angiotensin AT<sub>1</sub> and AT<sub>2</sub> receptors causing smooth muscle contraction and the release of aldosterone, prostacyclin, and catecholamines. The renin-angiotensin-aldosterone system plays an important role in the control of arterial pressure including the sodium balance.

### Atrial natriuretic peptide

Atrial natriuretic peptide (ANP) is released from atrial granules. It produces natriuresis, diuresis and a modest decrease in blood pressure, while decreasing plasma renin and aldosterone. Natriuretic peptides also alter synaptic transmission from the osmoreceptors. ANP is released as a result of the stimulation of atrial stretch receptors. ANP concentrations are increased by raised filling pressures and in patients with arterial hypertension and left ventricular hypertrophy as the wall of the left ventricle participates in the secretion of ANP.

### Eicosanoids

Arachidonic acid metabolites alter blood pressure through direct effects on vascular smooth muscle tone and interactions with other vasoregulatory systems: autonomic nervous system, renin-angiotensin-aldosterone system, and other humoral pathways. In hypertensive patients, vascular endothelial cell dysfunction could lead to reduction in endothelium-derived relaxing factors such as nitric oxide, prostacyclin, and endothelium-derived hyperpolarizing factor, or increased production of contracting factors such as endothelin-1 and thromboxane A<sub>2</sub>.

### Kallikrein-kinin systems

Tissue kallikreins act on kininogen to form vasoactive peptides. The most important is the vasodilator bradykinin. Kinins play a role in the regulation of renal blood flow and water and sodium excretion. ACE inhibitors decrease the breakdown of bradykinin into inactive peptides.

### Endothelial mechanisms

Nitric oxide (NO) mediates the vasodilatation produced by acetylcholine, bradykinin, sodium nitroprusside and nitrates. In hypertensive patients, endothelial-derived relaxation is inhibited. The endothelium synthesizes endothelins, the most powerful vasoconstrictors. The generation of, or sensitivity to, endothelin-1 is no greater in hypertensive than it is in normotensive subjects. Nonetheless, the deleterious vascular effects of endogenous

endothelin-1 may be accentuated by reduced generation of nitric oxide caused by hypertensive endothelial dysfunction.

### Adrenal steroids

Mineralo- and glucocorticoids increase blood pressure. This effect is mediated by sodium and water retention (mineralocorticoids) or increased vascular reactivity (glucocorticoids). In addition, glucocorticoids and mineralocorticoids increase vascular tone by upregulating the receptors of pressor hormones such as angiotensin II.

### Renomedullary vasodepression

Renomedullary interstitial cells, located mainly in the renal papilla, secrete an inactive substance medullipin I. This lipid is transformed in the liver into medullipin II. This substance exerts a prolonged hypotensive effect, possibly by direct vasodilatation, inhibition of sympathetic drive in response to hypotension, and a diuretic action. It is hypothesized that the activity of the renomedullary system is controlled by renal medullary blood flow.

### Sodium and water excretion

Sodium and water retention are associated with an increase in blood pressure. It is postulated that sodium, via the sodium-calcium exchange mechanism, causes an increase in intracellular calcium in vascular smooth muscle resulting in increased vascular tone.

The primary cause of sodium and water retention may be an abnormal relationship between pressure and sodium excretion resulting from reduced renal blood flow, reduced nephron mass, and increased angiotensin or mineralocorticoids.

### Pathophysiology

Hypertension is a chronic elevation of blood pressure that, in the long-term, causes end-organ damage and results in increased morbidity and mortality. Blood pressure is the product of cardiac output and systemic vascular resistance. It follows that patients with arterial hypertension may have an increase in cardiac output, an increase in systemic vascular resistance, or both. In the younger age group, the cardiac output is often elevated, while in older patients increased systemic vascular resistance and increased stiffness of the vasculature play a dominant role. Vascular tone may be elevated because of increased  $\alpha$ -adrenoceptor stimulation or increased release of peptides such as angiotensin or endothelins. The final pathway is an increase in cytosolic calcium in vascular smooth muscle causing vasoconstriction. Several growth factors, including angiotensin and endothelins, cause an increase in vascular smooth muscle mass termed vascular remodelling. Both an increase in systemic vascular resistance and an increase in vascular stiffness augment the load imposed on the left ventricle; this induces left ventricular hypertrophy and left ventricular diastolic dysfunction.

In youth, the pulse pressure generated by the left ventricle is relatively low and the waves reflected by the peripheral vasculature

occur mainly after the end of systole, thus increasing pressure during the early part of diastole and improving coronary perfusion. With ageing, stiffening of the aorta and elastic arteries increases the pulse pressure. Reflected waves move from early diastole to late systole. This results in an increase in left ventricular afterload, and contributes to left ventricular hypertrophy. The widening of the pulse pressure with ageing is a strong predictor of coronary heart disease.

The autonomic nervous system plays an important role in the control of blood pressure. In hypertensive patients, both increased release of, and enhanced peripheral sensitivity to, norepinephrine can be found. In addition, there is increased responsiveness to stressful stimuli. Another feature of arterial hypertension is a resetting of the baroreflexes and decreased baroreceptor sensitivity. The renin-angiotensin system is involved at least in some forms of hypertension (e.g. renovascular hypertension) and is suppressed in the presence of primary hyperaldosteronism. Elderly or black patients tend to have low-renin hypertension. Others have high-renin hypertension and these are more likely to develop myocardial infarction and other cardiovascular complications.

In human essential hypertension, and experimental hypertension, volume regulation and the relationship between blood pressure and sodium excretion (pressure natriuresis) are abnormal. Considerable evidence indicates that resetting of pressure natriuresis plays a key role in causing hypertension. In patients with essential hypertension, resetting of pressure natriuresis is characterized either by a parallel shift to higher blood pressures and salt-insensitive hypertension, or by a decreased slope of pressure natriuresis and salt-sensitive hypertension.

### Consequences and complications of hypertension

The cardiac consequences of hypertension are left ventricular hypertrophy and coronary artery disease. Left ventricular hypertrophy is caused by pressure overload and is concentric. There is an increase in muscle mass and wall thickness but not ventricular volume. Left ventricular hypertrophy impairs diastolic function, slowing ventricular relaxation and delaying filling. Left ventricular hypertrophy is an independent risk factor for cardiovascular disease, especially sudden death. The consequences of hypertension are a function of its severity. There is no threshold for complications to occur as elevation of blood pressure is associated with increased morbidity throughout the whole range of blood pressure (Table 1).

Coronary artery disease is associated with, and accelerated by, chronic arterial hypertension, leading to myocardial ischaemia and myocardial infarction. Indeed, myocardial ischaemia is much more frequent in untreated or poorly controlled hypertensive patients than in normotensive patients. Two main factors contribute to myocardial ischaemia: a pressure related increase in oxygen demand and a decrease in coronary oxygen supply resulting from associated atheromatous lesions. Hypertension is a significant risk factor for death from coronary artery disease.

**Table 1** Stages of hypertension (Joint National Committee VI Guideline)

Stage	Systolic	Diastolic
Optimal	<120	<80
Normal	120–129	80–84
High-normal	130–139	85–89
HT stage 1	140–159	90–99
HT stage 2	160–179	100–109
HT stage 3	>180	>110

Systolic and diastolic pressures given in mm Hg.  
HT, hypertension.

Heart failure is a consequence of chronic pressure overload. It may start as diastolic dysfunction and progresses to overt systolic failure with cardiac congestion. Strokes are major complications of hypertension; they result from thrombosis, thrombo-embolism, or intracranial haemorrhage. Renal disease, initially revealed by micro-albuminaemia may progress slowly and becomes evident in later years.

### Long-term treatment of hypertension

All anti-hypertensive drugs must act by decreasing the cardiac output, the peripheral vascular resistance, or both. The classes of drugs most commonly used include the thiazide diuretics,  $\beta$ -blockers, ACE inhibitors, angiotensin II receptors antagonists, calcium channel blockers,  $\alpha$ -adrenoceptor blockers, combined  $\alpha$ - and  $\beta$ -blockers, direct vasodilators, and some centrally acting drugs such as  $\alpha_2$ -adrenoceptor agonists and imidazoline  $I_1$  receptor agonists.

Life-style modification is the first step in the treatment of hypertension; it includes moderate sodium restriction, weight reduction in the obese, decreased alcohol intake, and an increase in exercise. Drug therapy is necessary when the above measures have not been successful or when hypertension is already at a dangerous stage (Stage 3) when first recognized.

### Drug therapy

#### Diuretics

Low-dose diuretic therapy is effective and reduces the risk of stroke, coronary heart disease, congestive heart failure, and total mortality. Whilst thiazides are most commonly used, loop diuretics are also used successfully and the association with a potassium sparing diuretic reduces the risk of both hypokalaemia and hypomagnesaemia. Even in small doses diuretics potentiate other anti-hypertensive drugs. The risk of sudden death is reduced when potassium-sparing diuretics are used. In the long-term, spironolactones reduce morbidity and mortality in patients with heart failure that is a typical complication of long-standing hypertension.

#### Beta-blockers

High sympathetic tone, angina, and previous myocardial infarction are good reasons for using  $\beta$ -blockers. As a low dose minimizes the risk of fatigue (an unpleasant effect of  $\beta$ -blockade)



addition of a diuretic or a calcium channel blocker is often beneficial. However,  $\beta$ -blockade therapy is associated with symptoms of depression, fatigue, and sexual dysfunction. These side-effects have to be taken into consideration in the evaluation of the benefits of treatment.

Over the past few years  $\beta$ -blockers have been used increasingly frequently in the management of heart failure, a known complication of arterial hypertension. They are effective but their introduction in the presence of heart failure has to be very cautious, starting with very low doses to avoid an initial worsening of heart failure.

### Calcium channel blockers

Calcium channel blockers can be divided into dihydropyridines (e.g. nifedipine, nimodipine, amlodipine) and non-dihydropyridines (verapamil, diltiazem). Both groups decrease peripheral vascular resistance but verapamil and diltiazem have negative inotropic and chronotropic effects. Short-acting dihydropyridines such as nifedipine cause reflex sympathetic activation and tachycardia, while long-acting drugs such as amlodipine and slow-release preparations of nifedipine cause less sympathetic activation. Short-acting dihydropyridines appear to increase the risk of sudden death. However, the systolic hypertension in Europe (SYST-EUR) trial which compared nitrendipine with placebo had to be stopped early because of significant benefits of active therapy.

Calcium channel blockers are effective in the elderly and may be selected as monotherapy for patients with Raynaud's phenomenon, peripheral vascular disease, or asthma, as such patients do not tolerate  $\beta$ -blockers. Diltiazem and verapamil are contraindicated in heart failure. Nifedipine is effective in severe hypertension and can be used sublingually; there is need for caution because of the risk of excessive hypotension. Calcium channel blockers are often associated with  $\beta$ -blockers, diuretics and/or ACE inhibitors.

### Angiotensin converting enzyme inhibitors

ACE inhibitors are increasingly being used as first line therapy. They have relatively few side-effects and contraindications except bilateral renal artery stenoses. Though ACE inhibitors are effective in unilateral renovascular hypertension, there is risk of ischaemic atrophy. Therefore, angioplasty or surgical renal artery reconstruction are preferable to long-term purely medical therapy. ACE inhibitors are first choice agents in diabetic hypertensive patients as they slow down the progression of renal dysfunction. In hypertension with heart failure, ACE inhibitors are also first choice drugs. The HOPE trial has shown that ramipril reduced the risk of cardiovascular events even in the absence of hypertension. Thus, this ACE inhibitor may exert a protective effect by mechanisms other than the reduction in blood pressure.

### Angiotensin II receptor blockers

As angiotensin II stimulates  $AT_1$ -receptors that cause vasoconstriction, angiotensin  $AT_1$ -receptor antagonists are effective

antihypertensive drugs. Losartan, valsartan and candesartan are effective and cause less coughing than ACE inhibitors.

The LIFE study is the most recent landmark trial in hypertension. More than 9000 patients were randomized to receive either the angiotensin receptor antagonist losartan or a  $\beta$ -blocker (atenolol). Patients in the losartan arm exhibited better reduction of mortality and morbidity, owing to greater reduction in strokes. Losartan was also more effective in reducing left ventricular hypertrophy, an independent powerful risk factor for adverse outcome. In patients with isolated systolic hypertension, the superiority of losartan over atenolol was even more pronounced than in those with systolic and diastolic hypertension. These favourable results led to an editorial entitled: 'Angiotensin blockade in hypertension: a promise fulfilled'. It must be noted that the comparator in the LIFE study was a  $\beta$ -blocker, and that, in the past,  $\beta$ -blockers were found to be no better than placebo in the elderly.

### $\alpha_1$ -Adrenergic blockers

Free from metabolic side-effects, these drugs reduce blood cholesterol and reduce peripheral vascular resistance. Prazosin is shorter acting than doxazosin, indoramin and terazosin. These drugs are highly selective for  $\alpha_1$ -adrenoceptors. Drowsiness, postural hypotension, and occasionally tachycardia, can be troublesome. Fluid retention may require the addition of a diuretic. Phenoxybenzamine is a non-competitive  $\alpha$ -adrenoceptor agonist used (in association with a  $\beta$ -blocker) in the management of patients with pheochromocytoma, though recently doxazosin has been used successfully.

### Direct vasodilators

Hydralazine and minoxidil are directly acting vasodilators. Their usage has declined because of the potential for serious side-effects (lupus syndrome with hydralazine, hirsutism with minoxidil).

### Central adrenergic inhibitors

Methyldopa is both a false neurotransmitter and  $\alpha_2$ -adrenoceptor agonist. Clonidine and dexmedetomidine are agonists at centrally located  $\alpha_2$ -adrenoceptors. The selectivity for  $\alpha_2$ - vs  $\alpha_1$ -adrenoceptors is greatest for dexmedetomidine (1620:1), followed by clonidine (220:1), and least for  $\alpha$ -methyldopa (10:1). Both clonidine and dexmedetomidine make the circulation more stable, reduce the release of catecholamines in response to stress, and cause sedation such that dexmedetomidine is now used for sedation in intensive care units.

Moxonidine is representative of a new class of antihypertensive agents acting on imidazoline<sub>1</sub> receptors ( $I_1$ ). Moxonidine reduces sympathetic activity by acting on centres in the rostral ventral lateral medulla, thereby reducing peripheral vascular resistance.

### Natriuretic peptides

Natriuretic peptides play a role in the control of vascular tone and interact with the renin-angiotensin-aldosterone system. By inhibiting their degradation, peptidase inhibitors make these naturally

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