Special review

Hypertension in the Critically Ill Patient

R. SANTHI, L. I. G. WORTHLEY
Department of Critical Care Medicine, Flinders University of South Australia, Adelaide, SOUTH AUSTRALIA

ABSTRACT

Objective: *To review the management of persistent hypertension and hypertensive crisis in the critically ill patient.*

Data sources: *A review of articles reported on hypertension and the critically ill patient.*

Summary of review: *Hypertension is defined as a basal systolic blood pressure of greater than 140 mmHg or diastolic blood pressure of greater than 90 mmHg (MAP > 105 mmHg), irrespective of age and is based on the average of two or more readings on two or more occasions over a period of four weeks. While a mean arterial pressure in the critically ill up to a value of 135 mmHg may be tolerated for some hours, in patients with dissecting aortic aneurysm, cardiac failure, angina, acute myocardial infarction, pre-eclampsia and following cardiac, vascular or cerebral surgery a mean arterial blood pressure of > 90 mmHg or greater should be lowered by up to 30% urgently.*

A hypertensive crisis may be defined as a MAP > 160 mmHg and can be caused by phaeochromocytoma, sympathomimetic overdose, malignant hypertension or autonomic hyper-reactivity secondary to tetanus. Treatment requires direct intra-arterial monitoring and an initial reduction in mean arterial pressure by no greater than 30%. While management of the primary condition (e.g. surgical removal of a phaeochromocytoma, delivery or termination of the pregnancy) may also be necessary, infusions of sodium nitroprusside, phentolamine, hydralazine or esmolol usually require supplementation with oral agents (e.g. angiotensin-converting enzyme inhibitors, beta-adrenergic receptor antagonists and calcium-channel blockers) for long-term management.

Conclusions: *A mean arterial pressure in the critically ill is often tolerated up to a value of 135 mmHg for some hours. However in some disorders (e.g. dissecting aortic aneurysm, cardiac failure, angina, acute myocardial infarction, pre-eclampsia or eclampsia and following cardiac, vascular or cerebral surgery) a mean arter-ial blood pressure of 90 mmHg or greater should be treated urgently.* (**Critical Care and Resuscitation 2003; 5: 24-42**)

Key words: Hypertension, critically ill, phaeochromocytoma, pregnancy-induced hypertension, malignant hypertension

Hypertension is defined as a basal systolic blood pressure of greater than 140 mmHg or diastolic blood pressure of greater than 90 mmHg (MAP > 105 mmHg) irrespective of age, and is based on the average of two or more readings on two or more occasions over a period of four weeks.[1] It is classified as 'mild' or 'moderate and severe' (Table 1), and is either primary (i.e. 'essential' and has no identifiable aetiology, other than the disorder tends to run in families) or secondary (i.e. has an identifiable cause, see Table 2).[2,3] While blood pressure is directly dependent on cardiac output and peripheral resistance, hypertension is almost always

Correspondence to: Dr. R. Santhi, Department of Critical Care Medicine, Flinders Medical Centre, Bedford Park, South Australia 5042

Table 1. Classification of blood pressure for adults

	Systolic (mmHg)		*Diastolic (mmHg)*	*MAP (mmHg)*
Normotension	< 140	and	< 90	< 105
Optimal	< 120	and	< 80	< 95
Normal	< 130	and	< 85	< 100
High normal	130 - 139	or	85 - 89	100 - 105
Hypertension				
Mild (stage 1)	140 - 159	or	90 - 99	105 - 120
Moderate (stage 2)	160 -179	or	100 - 109	120 - 135
Severe (stage 3)	≥ 180	or	≥ 110	> 135
Isolated systolic (IS)	≥ 160	and	< 90	
Borderline IS	140 - 160	and	< 90	

Table 2. Causes of secondary hypertension

Renal
- Renal artery stenosis
- Glomerulonephritis
- Pyelonephritis, hydronephrosis, polycystic kidneys
- SLE, scleroderma, polyarteritis nodosa
- Renin secreting tumour

Endocrine
- Adrenocortical disease
  - Conn's syndrome
  - primary aldosteronism
  - Cushing's disease
- Phaeochromocytoma
- Hyperparathyroidism, hypercalcaemia
- Hypothyroidism
- Acromegaly
- Drugs
  - oral contraceptives, corticosteroids, monoamine oxidase inhibitors cyclosporine, liquorice NSAIDs sympathomimetics (e.g. appetite suppressants, nasal decongestants)

Miscellaneous
- Coarctation of the aorta
- Pre-eclampsia
- Dysautonomia (associated with tetanus, acute porphyria)

due to an increase in peripheral vascular resistance.[4]

In the critically ill patient, blood pressure measurements are often recorded directly from the radial, brachial or femoral artery and treatment depends on patient's underlying disorder as well as the level recorded. For example, a patient with a diastolic blood pressure that is consistently greater than 115 mmHg (MAP 135 mmHg) and where no end-organ damage exists, antihypertensive treatment is used to reduce the blood pressure (i.e. diastolic blood pressure < 115 mmHg or MAP < 135 mmHg) within 24 h. However, where there is progressive end-organ damage such as cardiac failure, renal failure, retinal changes or cerebral dysfunction (hypertensive encephalopathy), a mean arterial blood pressure of > 135 mmHg should be lowered within the hour.[5,6]

In some disorders (e.g. dissecting aortic aneurysm, cardiac failure, angina, acute myocardial infarction, pre-eclampsia or eclampsia and following cardiac, vascular or cerebral surgery) a mean arterial blood pressure of > 90 mmHg should also be lowered (i.e. MAP lowered by up to 30%) urgently.

While hypertension *per se* is often asymptomatic, an hypertensive crisis may present clinically with an acute cardiovascular disorder (e.g. pulmonary oedema) or an encephalopathy and usually occurs when the blood pressure is consistently greater than 200/140 mmHg (MAP > 160 mmHg). The causes of a hypertensive crisis are listed in Table 3.[7,8]

Table 3. Causes of hypertensive crisis

- Phaeochromocytoma
- Eclampsia, pre-eclampsia
- Malignant hypertension
- Sympathomimetic overdose (e.g. cocaine, amphetamines, phencyclidine, LSD)
- Interactions with MAOI (e.g. tyramine)
- Clonidine withdrawal
- Autonomic hyper-reactivity (e.g. tetanus, porphyria, baroreflex failure)

Phaeochromocytoma

Phaeochromocytomas are catecholamine-producing tumours, 80% of which are found as a single benign adrenal tumour (many of which favour the right side), 10% are bilateral (particularly familial phaeochromocytomas), and 10% are extra-adrenal (usually in the abdomen in association with the coeliac, superior mesenteric, or inferior mesenteric ganglia; approximately 1% are in the thorax, 1% are within the urinary bladder, and 1% are in the neck in association with the sympathetic ganglia or the extracranial branches of the 9th and 10th cranial nerves), and approximately 10% are malignant.

While it was believed that approximately 10% were familial (inherited usually as an autosomal dominant, either alone or in combination with other abnormalities, e.g. multiple endocrine neoplasia or von Recklinghausen's neurofibromatosis), it is currently thought that up to 25% of patients with 'sporadic' phaeochromocytomas have germline mutations of one of the 4 susceptibility genes for phaeochromocytoma.[9]

Phaeochromocytomas occur in 0.04% of hypertensive patients.[10] Seventy per cent of the tumours secrete adrenaline and noradrenaline, the remaining 30% secrete noradrenaline only. Related catecholamine secreting tumors (producing similar clinical syndromes) include carotid body chemodectomas and postganglionic sympathetic neuron ganglioneuromas.

Clinical features

Headache, palpitations and diaphoresis are the three commonest symptoms associated with a phaeochromocytoma.

Headaches. During the hypertensive episodes, a severe pounding headache occurs which is bilateral and frontal or occipital or both. The headache is sudden in onset and short in duration (e.g. 15 min); it may awaken the patient, cause vomiting and is often relieved by standing.

Palpitations (with or without tachycardia). Palpitations are episodic in nature. If a bradycardia occurs during an attack it suggests a noradrenaline secreting extra-adrenal tumour.[11]

Diaphoresis. Episodes of excessive or inappropriate perspiration occur suddenly. They may be nocturnal and may be limited to the scalp or upper part of the body.

Less common symptoms. These include heat intolerance, nervousness, anxiety, a sense of impending doom, tremor, facial pallor, nausea, vomiting, weakness, fatigue, chest or abdominal pains, dyspnoea (patients may develop pulmonary oedema during an attack), polyuria, fever, and weight loss. Flushing is rare although not rare enough to cast doubt on the diagnosis,[11] also it is not unknown for both phaeochromocytoma and carcinoid tumour to exist together.[12]

Hypertension. This is either continuous or paroxysmal and is the most consistent manifestation of this disorder. In 50% of patients the hypertension is paroxysmal, occurring either infrequently (i.e. once or twice a year), or many times during a day. Exertion, emotional stress or increase in intra-abdominal pressure frequently precipitates the attacks. The paroxysms are usually severe, thus the diagnosis should always be considered if the systolic pressure increases to 300 mmHg or greater. The duration of the hypertensive paroxysm is usually short-lived (i.e. < 1 h) with symptom-free intervals occurring between the attacks, distinguishing it from chronic anxiety states. The patient may also have postural hypotension between the attacks.

Patients may also present as a clinical syndrome. For example,

An acute cardiac syndrome

a. Cardiomyopathy (acute or chronic), myocardial infarction or a myocardial infarction-like syndrome may occur, due to severe catecholamine-induced increase in myocardial contractility, peripheral vasoconstriction (which may be severe enough to produce Raynaud's phenomenon and peripheral gangrene) and coronary vasospasm. In these circumstances the chest pain usually occurs during the attack rather than preceding it, thereby differentiating it from a primary myocardial infarct.
b. Cardiac arrhythmias (e.g. sinus tachycardia, sinus bradycardia, paroxysmal supraventricular tachycardia, atrial fibrillation, atrial flutter, ventricular tachycardia).
c. Fulminant cardiac failure with severe pulmonary oedema may occur.
d. Cardiogenic shock due to myocardial infarction or an acute catecholamine-induced myocarditis may also occur,[13,14] and is an ominous sign.
e. Prolonged QTc interval with (rarely) torsade de pointes.[15]

A multisystem crisis

This presents as a multisystem failure (i.e. renal, hepatic, cardiac and respiratory failure) with pyrexia, hypertension or hypotension and encephalopathy.[16]

The differential diagnosis of phaeochromocytoma includes, thyroid crisis, hypoglycaemia (e.g. insulinoma), panic attack, hyperventilation, withdrawal of alcohol, opiate or clonidine, porphyria, overdosage with

sympathomimetic agents and monoamine oxidase inhibitors with tyramine-induced hypertensive crisis.

Investigations

Nonspecific tests. Patient may have hypokalaemia, hypercalcaemia (even in the absence of parathyroid hyperplasia or adenoma), hyperglycaemia (approximately 50% have carbohydrate intolerance due to suppression of insulin and increased hepatic glycogenolysis), lactic acidosis[12] and hypophosphataemia. An elevated haematocrit is often present due to a decrease in plasma volume.

Specific tests. The diagnosis is confirmed by biochemical demonstration of excess catecholamine excretion, for example:

a) *Twenty-four hour urinary 3 methoxy-4-hydroxymandelic acid ('VMA'), metanephrine or catecholamine levels*
Due to the short half-life and spasmodic nature of liberation of catecholamines, 24 h urine catecholamine values provide a better diagnostic test than plasma catecholamine values.[17] Urinary noradrenaline is normally less than 790 pmol/24 h. In patients with phaeochromocytoma it is usually > 1600 pmol/24 h. The urine collection container requires 10 mL of 6 *N* HCl to keep the pH below 3 to preserve catecholamine levels. Urine metanephrines and VMA estimations do not require acidification, although numerous foods and medications may influence the assay and may give falsely high values.

b) *Plasma catecholamine levels*
For accurate plasma catecholamine estimations, the patient is required to have a sampling venous cannula inserted and to rest in a supine position for 30 min before the blood sample is collected. Plasma levels of total catecholamines (adrenaline and noradrenaline) of greater than 2000 pg/mL (11.82 nmol/L) are pathognomonic of phaeochromocytoma.[18]

If levels of between 1000 and 2000 pg/mL are found, a clonidine-suppression test (0.3 mg of clonidine intravenously, measuring plasma catecholamines 2 - 3 h later) may be performed.[18] The latter test is based on the principle that normal elevation of serum catecholamines is mediated through activation of the sympathetic nervous system, and is suppressible by the centrally acting alpha$_2$ adrenergic agonist, clonidine, thereby reducing plasma catecholamines to less than 500 pg/mL (2.95 nmol/L) in patients without phaeochromocytoma. If the urinary or plasma levels are equivocal, a CT of the abdomen should be performed.[19]

c) *Abdominal CT scan*
An abdominal CT scan has a localising precision of 96% for tumours greater than 1 cm in size.[18]

d) *Selective arteriography, venography and venous catecholamine levels*
If the abdominal CT fails to localise the tumour then selective angiography or venography with selective caval sampling for catecholamine levels may be performed. However, the latter requires the same preparation as the preoperative preparation for tumour removal; thus, these techniques are often only used if an extra-adrenal tumour is suspected.

e) *Scintiscan*
^{131}I-metaiodobenzyl guanidine (MIGB) is selectively taken up by adrenergic cells and may be used to localise the phaeochromocytoma on scintiscan. This compound may also be used to treat malignant phaeochromocytomas with secondary deposits.[18]

f) *Provocative testing*
This is hazardous, although it is sometimes performed if the patient's history is suggestive of a phaeochromocytoma, the diastolic blood pressure is no greater than 110 mmHg, a lesion is demonstrated on CT and the patient's urinary and plasma levels are not diagnostic. A provocative test is performed using 1 - 2 mg of glucagon intravenously and close monitoring of blood pressure. Infusions of sodium nitroprusside or phentolamine and propranolol or esmolol are close at hand to suppress excessive hypertension or tachycardia, should they occur.

Treatment

Medical management of a hypertensive crisis

During a hypertensive crisis, a 10 mg intravenous bolus of phentolamine is administered followed by an infusion at 0.5 - 2.0 mg/min. If a severe tachycardia is present then atenolol or metoprolol may be infused at 1 mg/min up to 10 - 20 mg. Alpha-adrenergic blockade should always be administered before beta-adrenergic blockade (particularly when using a non-selective beta-blocker such as propranolol), otherwise peripheral and coronary vasoconstriction, inhibition of skeletal muscle beta adrenergic vasodilation, and a reduction in myocardial contractility may precipitate pulmonary oedema and myocardial ischaemia.[20]

Surgical removal

Phaeochromocytoma is cured by surgical removal. This requires the correct preoperative preparation with alpha-blockade to minimise mortality.

In emergency cases, maximum alpha-blockade is provided by intravenous (or oral) phenoxybenzamine, 100 mg in 1 h administered 24 h before the operation, although 1 - 2 units of blood or 1 - 2 L of plasma is also required during this 24 h period to maintain the circulating blood volume (as estimated by pulse, blood pressure, central venous or pulmonary wedge pressure measurements).

In elective cases, maximum alpha-blockade is provided by administering oral phenoxybenzamine over 1 - 2 weeks and monitoring its effect by supine and erect blood pressure measurements. This may be achieved by administering oral phenoxybenzamine 20 mg/day (usually in divided doses to reduce the postural hypotensive effect), and increasing by 20 mg/day after 3 - 5 days up to 40 - 100 mg/day (or 1 mg/kg/day) daily for 7 days preoperatively, with the patient maintaining the blood volume by normal fluid retention mechanisms during this period.

Treatment with beta-blockade preoperatively is not necessary and it is only required intraoperatively if there is clinically significant tachycardia or arrhythmias. Sodium nitroprusside or phentolamine infusions are often used intraoperatively to manage any undesirable rises in blood pressure. Vecuronium, fentanyl and nitrous oxide are recommended as the anaesthetic agents of choice for the surgical removal of phaeochromocytoma as they do not provoke catecholamine release, do not release histamine and have no autonomic effects at clinical plasma concentrations.[21] Monitoring of the ECG, arterial blood pressure, PAoP, pulmonary artery pressure, right atrial pressure and cardiac output are required during surgery.

Pregnancy-induced hypertension, pre-eclampsia and eclampsia

Pregnancy-induced hypertension (PIH) is defined as the development of a systolic blood pressure $\geq$ 140 or a diastolic blood pressure $\geq$ 90 mmHg or a rise in systolic blood pressure $\geq$ 25 mmHg or diastolic blood pressure $\geq$ 15 mmHg from first-trimester levels, occurring in a primigravida, after 20 weeks gestation, in a patient with no known history of hypertension or renal disease and in a patient whose pressure returns to normal within 3 months postpartum.[22-27]

Pre-eclampsia is a more severe form of PIH and is associated with proteinuria, hyperuricaemia or subcutaneous oedema. Grand mal convulsions distinguish eclampsia from pre-eclampsia. Eclampsia is not complicated by papilloedema or retinal haemorrhages; thus it is not a form of malignant hypertension but a form of hypertensive encephalopathy.

The HELLP syndrome, characterised by liver dysfunction, coagulopathy and haemolysis (Haemolysis, Elevated Liver enzymes, Low Platelets) is a variant of pre-eclampsia and is associated with an increase in morbidity, although pulmonary oedema, renal failure, hepatic failure, cerebral haemorrhage and cerebral oedema may also occur in patients with pre-eclampsia (or eclampsia) to increase maternal and fetal morbidity.[28]

During normal pregnancy there is a fall in blood pressure (due to a decrease in peripheral resistance) and an increase in blood volume (peaking about 40% above baseline by the third trimester) and ECF volume. In PIH, pre-eclampsia, eclampsia and HELLP syndrome there is an increase in peripheral resistance and a decrease in blood volume with an increase in ECF volume caused by an increase in capillary permeability. These disorders are probably a spectrum of the same disease which best fits the category of a pregnancy-induced haemolytic uraemic syndrome in which a placental endothelial cytotoxic factor causes platelet aggregation and fibrin deposits in various vascular beds.[29,30]

Clinical features

The clinical features of pre-eclampsia include a rising blood pressure, abdominal pain, headaches, vomiting, hyper-reflexia, clonus, and clouded sensorium. If seizure activity occurs (e.g. visual scintillation, or focal or general seizures), the diagnosis is eclampsia.

Investigations

The biochemical features of pre-eclampsia include proteinuria, renal impairment, disseminated intravascular coagulation (DIC) and hepatic dysfunction.

Treatment

The management of PIH includes bed rest, oral antihypertensive agents, if the blood pressure remains elevated, and timely delivery (to maximise maternal and fetal wellbeing).

Hypertension may be managed by using beta-adrenergic blockers (e.g. metoprolol, atenolol, labetalol), hydralazine or calcium-channel blockers. ACE inhibitors are contraindicated (they may lead to neonatal renal failure and foetal death), as are diuretics and sedatives. For urgent management of hypertension, diazoxide (which, like minoxidil, opens K_{ATP} channels, causing hyperpolarisation and closure of the voltage operated calcium channels, thereby relaxing the vascular smooth muscle cell)[31] 30 mg intravenously in repeated doses, or 5 mg hydralazine intravenously every 20 min, until the MAP is reduced by no greater than 30% in the first 24 h, can be used (> 30% reduction in MAP requires monitoring of foetal blood flow).

However, continuous management of hypertension and hyper-reflexia, in patients who are admitted to

hospital for delivery, requires intravenous magnesium sulphate using a loading dose of 4 g (16 mmol) over 5 min, followed by 1 g/h (i.e. 4 mmol/h) and continued for 24 h after delivery. This halves the risk of eclampsia,[32] is more effective than phenytoin in preventing eclampsia[33] and is more effective than diazepam or phenytoin in controlling eclamptic seizures.[34] If renal failure occurs, the magnesium infusion is modified using plasma magnesium levels. Therapeutic plasma levels of magnesium range between 2 and 3.5 mmol/L, and should be monitored 6 to 12-hourly. If intravenous saline or albumin solutions are considered necessary, then a central venous catheter or Swan-Ganz catheter may also be required for close monitoring. Intravenous diazepam (5 - 10 mg) may be administered to control acute seizures.

Delivery or termination of the pregnancy is the only known cure for PIH.[35] Warning signs of impending eclampsia such as sustained clonus, hyper-reflexia, severe headache, photophobia, drowsiness, or coma are indications for delivery. Other indications of progressive disease, such as rising uric acid, decreasing platelet count (indicative of progressive DIC) and progressive renal impairment, are relative indications for delivery and need to be considered in the context of period of gestation, foetal viability, foetal growth, foetal distress and overall maternal condition.

Malignant hypertension

Malignant hypertension is a condition caused by generalised arteriolar fibrinoid necrosis (which is reversed by reduction of blood pressure), arising *de novo* or as a consequence of hypertension from any cause. It is characterised by cardiac failure, renal failure and hypertensive encephalopathy. The vascular changes are best observed in the fundus, as arteriolar spasm, retinal haemorrhages, retinal infarcts and papilloedema. Approximately 30% of patients with malignant hypertension have an underlying renovascular aetiology.[36] The blood pressure is usually greater than 200/140 mmHg (MAP > 160 mmHg) and if left untreated 90% of patients die within 1 year.

The clinical features are characteristically those of a hypertensive encephalopathy which include a severe headache, vomiting, visual disturbances (even transient blindness), transient paralysis, convulsions, stupor and coma, and will usually only occur in previously normotensive individuals if the MAP is 135 mmHg or greater or 160 mmHg or greater in previously hypertensive patients.[37] The diagnosis is confirmed by a negative CT scan (performed to exclude cerebrovascular haemorrhage with associated hypertension) and by the dramatic response to therapy within the first 12 - 24 h.[36,38]

Blood pressure should not be returned rapidly to normotensive levels because autoregulation levels are elevated, and lowering blood pressure levels below these levels (particularly in patients whose cerebral or coronary circulation is already compromised) may increase the risk of a thrombotic stroke or myocardial infarction.[39] While a mean arterial blood pressure of no greater than 90 mmHg (e.g. 130/70) with adequate coronary, cerebral and renal function is optimal, the MAP may be required to be greater than this to support myocardial, cerebral and renal function and should be rapidly reduced by no greater than 30% for the first 24 h, using sodium nitroprusside to supplement one of the agents listed in Table 4.[36] While glyceryl trinitrate may also be used (particularly when angina is present) it has only a mild to moderate effect on reducing blood pressure as its venodilating effect is greater than its arteriolar dilating effect. Sublingual nifedipine (10 mg 2 - 4-hourly) is no longer recommended as it is not associated with a reduction in mortality.[40]

Table 4. Drugs used to treat hypertensive emergencies

Drug	*Dosage i.v. infusion*	*Biological half-life*
Sodium nitroprusside	10 - 300 μg/min	2 min
Glyceryl trinitrate	10 - 200 μg/min	1.5 min
Phentolamine	500 - 2000 μg/min	10 - 30 min
Diazoxide	30 - 300 mg (bolus)	2 - 4 h
Hydralazine	5 - 40 mg hourly	4 h
Chlorpromazine	5 - 10 mg (bolus)	1 - 2 h

TREATMENT

The choice of drug often depends upon specific indications or contraindications and presence or absence of side-effects of drugs in the individual patient. Most patients should be treated with a single agent as the first-line therapy, for example an ACE inhibitor or beta-blocker (although one study found that a thiazide diuretic was more efficacious than beta-blockers as first line therapy in elderly patients with hypertension).[41]

Calcium antagonists are used less often in the management of hypertensive patients, as recent studies have concluded that calcium-channel-blockers, particularly in high doses and of the shorter acting dihydropyridine class (e.g. nifedipine, felodipine, nicardipine), increase the risk of myocardial infarction and increase mortality[42,43] (an effect which may not be true for the slower onset calcium-channel blockers e.g. verapamil, diltiazem, amlodipine and slow release nifedipine).[44,45] In hypertensive diabetic patients, treatment with nisoldipine (a long-acting calcium-channel blocker) is

associated with a higher incidence of fatal and non-fatal myocardial infarction when compared with enalapril.[46]

An ACE inhibitor in combination with a diuretic will control 85% of hypertensive patients and would appear to be the therapy of choice for the majority of hypertensive patients.[47,48] If a beta-blocker is used then one of the cardioselective beta-blockers is chosen (i.e. atenolol or metoprolol); these have antihypertensive effects due to their ability to reduce cardiac output, decrease central sympathetic tone, decrease renin release, reset baroreceptors and block prejunctional $beta_2$ adrenoreceptors (although blockade of prejunctional $beta_2$ adrenoreceptors is greater with nonselective beta-blockers). For significant hypertension (i.e. diastolic blood pressure > 100 mmHg), thiazide diuretics are often relegated to 'second line' therapy due to their low efficacy as a single agent and their side-effects of hypokalaemia, hypomagnesaemia, hyperglycaemia, hyperuricaemia and hyperlipidaemia. Also they should be used in combination with a potassium sparing agent as the risk of primary cardiac arrest is greater in patients treated with thiazide diuretics, than in patients who are treated with a combination of thiazide and potassium-sparing diuretic agents.[49] In one study of hypertensive patients, the alpha antagonist doxazosin was associated with a 25% higher rate of combined cardiovascular events and a two fold increase in heart failure compared with those receiving the thiazide diuretic chlorthalidone.[50]

In the critically ill patient, where direct blood pressure monitoring is present, intravenous antihypertensive treatment is often used to reduce the blood pressure, although this is often supplemented with enteral therapy to allow withdrawal of short acting antihypertensive agents and provide long term control of blood pressure.

Nitric oxide generators

Sodium nitroprusside

Sodium nitroprusside (SNP) is a direct acting arteriole and venodilating agent with a biological half-life of 2 min and no direct myocardial inotropic action.[51,52] Once infused SNP interacts with oxyhaemoglobin, dissociating immediately to form a small amount of methaemoglobin (to generate a methaemoglobin level of up to 10%, approximately 700 mg of SNP is required to be infused in less than 24 h) nitric oxide (which is responsible for the vasodilator effects) and five cyanide radicals.[53] The cyanide radicals may react immediately and nonenzymatically with methaemoglobin to form cyanomethaemoglobin which is considered non toxic (normal methaemoglobin concentrations of 0.5% are capable of binding cyanide released from 18 mg of sodium nitroprusside).[54] The free cyanide left is enzymatically converted in the liver by mitochondrial rhodanese (in the presence of thiosulphate) to thiocyanate. In humans, hepatic thiosulphate availability is the limiting factor in cyanide detoxification, and the maximum rate of thiocyanate production corresponds to a SNP infusion of 2 μg/kg/min up to a maximum total of 50 mg of SNP.[55] Serum hydroxocobalamin (vitamin B_{12}) levels decrease significantly during SNP infusions due to formation of cyanocobalamin, which is rapidly excreted. While vitamin B_{12} deficiency has not yet been described,[56,57] SNP should be avoided in patients with vitamin B_{12} deficiency, Leber's optic atrophy and tobacco amblyopia.[58]

Dosage. SNP is usually prepared as a solution containing 50 in 50 mL 5% dextrose (i.e. 1000 μg/mL, where a rate of 0.6 - 18 mL/h provides 10 - 300 μg/min), which is shielded from light (although cyanide release from SNP in 5% dextrose solution exposed to light for 8 h or protected from light exposure for 24 h, is insignificant[59]) and discarded after 24 h of use.

When it is used to control hypertension, it is administered as an initial dose of 25 - 50 μg/min (0.5 μg/kg/min) increasing by 25 - 50 μg/min increments every 10 min until the desired response is obtained. The dose usually ranges from 50 to 300 μg/min (0.7 - 4 μg/kg/min).[58] If adequate blood pressure control is not obtained at 150 μg/min, then other hypotensive agents (e.g. 2 - 10 mg atenolol intravenously) should be added, as SNP exceeding 2 μg/kg/min (150 μg/70 kg/min) causes cyanide accumulation. Rates exceeding 4 μg/kg/min (i.e. 300 μg/70 kg/min) may lead to cyanide toxicity within 3 h.[60] SNP should not be used for longer than 48 h.

Toxicity. SNP excess will lead to cyanide toxicity, which occurs at RBC cyanide levels of greater than 75 μg/100 mL. This characteristically causes metabolic acidosis, an increase in mixed venous PO_2 and often a progressive resistance to the hypotensive effect of SNP, although , encephalopathy, focal neurological abnormalities, coma and unexplained cardiopulmonary arrest may occur in the absence of metabolic acidosis.[61] Toxicity is likely to occur if total amounts of greater than 50 - 70 mg (i.e. 1 mg/kg) are used or when SNP rates exceed 2 μg/kg/min.[55] Hydroxocobalamin may significantly increase the capacity of the body to handle free cyanide ions by forming cyanocobalamin,[58] and intravenous hydroxocobalamin at 30 mg/h up to 100 mg has been used to prevent cyanide toxicity during SNP infusion.[62] If cyanide toxicity occurs, then the SNP infusion is discontinued and intravenous hydroxocobalamin is probably the treatment of choice,[63] although large doses are needed (e.g. it would take 2.5 g of

hydroxocobalamin to neutralise all the cyanide from 100 mg of sodium nitroprusside[64]).

Glyceryl trinitrate

Glyceryl trinitrate (nitroglycerin) is a direct-acting vasodilator which causes venodilation at lower doses and increasing arterial vasodilation at higher doses.[65] The release of nitric oxide from glyceryl trinitrate and intracellular vascular smooth muscle sulphydryl-donating thiols (e.g. cysteine, dithiothreitol, N-acetyl-cysteine) is an enzymatic process that probably requires sulphydryl-donating compounds as a cofactor.[53] Tolerance to intravenous glyceryl trinitrate develops rapidly after 18 - 24 h, and some believe that this can be reversed with intravenous N-acetylcysteine (200 mg/kg).[66,67] Others, however, have failed to confirm this effect.[68,69]

Intravenous glyceryl trinitrate has a biological half-life of 1.5 min, due to extensive nitrate extraction across the arteriovenous bed and rapid hepatic metabolism by the enzyme glutathione-organic nitrate reductase.

Dosage. A solution containing 50 - 150 mg of glyceryl trinitrate in 500 mL of 5% dextrose (i.e. 100 - 300 μg/mL) is prepared for intravenous administration. Because 40 - 80% of glyceryl trinitrate is adsorbed by plastics,[70] glass bottles and syringes are used. The infusion is initiated at a rate 5 μg/ min and increased 5 - 10 μg/min every 10 min until the desired response is achieved. The haemodynamic response depends upon the dose administered. For example, at a rate of 30 - 40 μg/min venodilation predominates, whereas at a rate of greater than 250 μg /min there is marked arterial dilation.[71] The average intravenous dose ranges from 70 - 80 μg/min.[72]

Toxicity. The side-effects of glyceryl trinitrate include, hypotension, tachycardia, headache, and increase in intracranial pressure (ICP) (it is contraindicated in patients who have raised ICP).[73] The rarer complications associated with glyceryl trinitrate include methaemoglobinaemia (which may occur with high dosages (e.g. > 7 μg/kg/min or 500 μg/min) or in patients with methaemoglobin reductase deficiencies, nitrate withdrawal (coronary artery spasm and even myocardial infarction has been described in industrial workers who have withdrawn from a prolonged nitrate exposure), reversible resistance to heparin anticoagulation,[74] hypoxaemia (due to pulmonary vasodilation and ventilation perfusion mismatch)[75] and propylene glycol intoxication (which presents with lactic acidosis and hyperosmolality particularly in patients with renal failure who have been on large intravenous doses of glyceryl trinitrate i.e. > 5 μg/kg/min for > 7 days).[76]

Hydralazine

Hydralazine is a direct-acting arterial vasodilator that has little venodilating effect. With prolonged high doses (e.g. > 200 mg/day or a total dose of 100 g or greater[77]) a lupus syndrome may occur. Hydralazine is either rapidly or slowly acetylated in the liver. Patients who have fast acetylation rates have an oral bioavailability of 30% and are less likely to develop lupus. Patients who have slow acetylation rates have an oral bioavailability of 50%. A reflex tachycardia usually occurs when the agent is used intravenously. Hydralazine also exerts a mild positive inotropic action.[51]

Hydralazine can be administered as a bolus of 5 - 20 mg and repeated after 1 h up to a maximum of 50 - 100 mg/24 h. It has an onset of action of 5 - 10 min, which peaks after 15 - 30 min and lasts for 4 - 6 h. The side-effects of hydralazine include, headache, tachycardia, angina, nausea, vomiting, rash, oedema, and lupus syndrome.

Thiazide diuretics

The thiazide diuretics (e.g. hydrochlorothiazide, chlorothalidone, bendrofluazide) inhibit an apical distal convoluted tubule epithelium Na^+:Cl^- cotransporter (i.e. Site III, where up to 10% of the filtered load of sodium is reabsorbed).[78] Metolazone shares the pharmacologic actions of thiazide diuretics, yet in contrast to the thiazides it also reduces proximal tubule sodium reabsorption and therefore has a greater diuretic effect. While indapamide has a mild diuretic action, it has a pronounced antihypertensive effect, largely by inhibiting the vascular smooth muscle slow component of delayed rectifier potassium current, and thereby reducing the inward Ca^{2+} current.[79]

The thiazides work in hypertension by causing peripheral vasodilation (an effect which is maximum at the lowest dose, e.g. 2.5 mg of bendrofluazide daily) rather than by their diuretic effect, and in this regard they are superior to loop diuretics.[80] Thiazides reduce urinary excretion of calcium by directly stimulating calcium uptake in the distal tubule and, through volume contraction, indirectly stimulating calcium uptake in the proximal tubule.

The side-effects include hypokalaemia (by increasing sodium delivery to the mineralocorticoid sensitive segment), azotaemia, hypomagnesaemia, hypercalcaemia, metabolic alkalosis, hyperglycaemia, hyperuricaemia (due to inhibition of renal urate excretion in the pars recta), pancreatitis, and, rarely and allergic reactions (e.g. erythema multiforme, photosensitivity, interstitial nephritis, thrombocytopenia and neutropenia).

The renin-angiotensin-aldosterone system inhibitors

Angiotensin converting enzyme (ACE) inhibitors

Angiotensin converting enzyme (ACE) is found on

the surface of all vascular endothelial cells and is responsible for the formation of angiotensin II as well as the inactivation of the vasodilator peptide, bradykinin (ACE is also involved in the degradation of substance P, neurokinins, and luteinising hormone releasing hormone).[81,82]

Angiotensin II acts on specific membrane receptors located on target organs and its biological effects are by mediated by two receptors, AT_1 and AT_2. The AT_1 receptor is a G-coupled membrane protein which activates phospholipase C and produces the secondary messengers inositol 1,4,5-triphosphate (which releases Ca^{2+} from the sarcoplasmic reticulum) and diacylglycerol (which activates protein kinase C), causing smooth muscle constriction. AT_1 receptor activation also causes vascular smooth muscle remodeling, catecholamine release (adrenal and presynaptic), vaso-pressin release, renal tubular sodium reabsorption and aldosterone release, it also inhibits baroreceptor sensitivity.[83,84] The function of the AT_2 receptor is not yet clear, although it has been postulated that it may be involved in the differentiation and proliferation of smooth muscle cells as well as being antiproliferative for endothelial cells.[84] The enzymes that destroy angiotensin II are collectively called angiotensinase and form a heptapeptide called angiotensin III. While angiotensin III has only about 40% of the pressor activity of angiotensin II, it has 100% of the aldosterone-stimulating activity.

The renin-angiotensin-aldosterone system may be inhibited at several levels: inhibition of renin release by the juxtaglomerular apparatus (e.g. beta adrenergic blockade, indomethacin), inhibition of the angiotensinogen-renin step by using monoclonal renin antibodies or angiotensinogen analogues (e.g. renin inhibitory peptides which compete with angiotensinogen for renin binding sites), conversion of angiotensin I to angiotensin II by ACE inhibitors, and angiotensin II receptor blockade (e.g. losartan) and aldosterone receptor blockade (e.g. spironolactone).[85]

ACE inhibitors cause:

1. A reduction in blood pressure due to a reduction in angiotensin II levels, a decrease in prejunctional release of noradrenaline in response to sympathetic nerve stimulation (caused by the reduction in angiotensin II levels) and an increase in bradykinin levels. The latter causes peripheral vasodilation (due to endothelial NO and prostacyclin release) and may be responsible for the hypotensive effect of captopril observed in anephric patients[86] and the reduction in myocardial oxygen consumption (due to bradykinin induced release of NO which in turn inhibits cytochrome oxidase) observed with ACE inhibitors.[87]

2. A reduction in aldosterone secretion from the zona glomerulosa which results in a mild natriuresis and a tendency towards K^+ retention. In patients with Na^+ depletion and high renin levels (i.e. renal artery stenosis, renovascular hypertension, hypovolaemia or diuretic therapy) a large reduction in blood pressure, and natriuretic and antikaliuretic effects may occur. In patients with low renin hypertension (which is usually associated with an increase in intravascular volume), the fall in blood pressure, natriuretic and antikaliuretic effects may be mild.

3. Renal vasodilation with a fall in filtration fraction due to a fall in post glomerular (efferent) arteriolar tone, which may lead to a reduction in GFR.[88] The rise in creatinine, with ACE inhibitors, may be a valuable clue of an undetected bilateral renal artery stenosis or renal artery stenosis in a single kidney (e.g. renal allograft).[89-91] Endogenous prostaglandins serve to maintain renal blood flow in low cardiac output states by dilating the afferent arteriole, and maintain GFR by increasing efferent vasoconstriction by stimulating the intrarenal release of renin. Therefore, prostaglandin inhibition in association with ACE inhibition leads to both afferent arteriole vasoconstriction and efferent arteriole vasodilation and reduction in GFR.[90] In patients with diabetic nephropathy, captopril reduces the risk of the combined endpoints of dialysis, transplantation and death by 50%.[92] In one study of patients with non-diabetic renal disease, combined treatment with an angiotensin-II receptor blocker (losartan 100 mg daily) and an angiotensin-converting-enzyme inhibitor (trandolapril 3 mg daily) retarded the progression of renal disease compared with monotherapy.[93]

4. A decrease in renin substrate levels.

5. An increase in renin and angiotensin I levels (which so far has not been reported to be associated with any abnormality).

Captopril and lisinopril are active compounds whereas enalapril, alacepril (prodrug of captopril), pentopril, fosinopril, perindopril, quinapril, trandolapril, cilazapril, benazepril and ramipril are prodrugs (i.e. remain inactive until converted by the liver into an active compound). The active form of the drug reach peak levels later with the prodrug (e.g. peak levels of captopril occur 90 min after captopril ingestion and 4 h after alacepril ingestion). The commonly used ACE inhibitors and their oral dosages are listed in Table 5.[94]

In comparison with the beta-blocking drugs, ACE inhibitors are not associated with drowsiness, sexual dysfunction, or Raynaud's phenomenon, and the autonomic reflexes are intact (i.e. heart rate and cardiac output response to exercise and the Valsalva manoeuvre are not altered[81]). In comparison to the direct vasodilators, ACE inhibitors are not associated with postural hypotensive effects or reflex tachycardia[95] (i.e.

reduction in cardiac work due to afterload reduction is not negated by tachycardia[96]). Also the hypotensive effects of diuretics are enhanced without inducing hypokalaemia because the secondary hyperaldosterone effects of diuretics are inhibited.[97]

Table 5. Dosage and pharmacokinetics of ACE inhibitors and AT receptor antagonists

Drug	*Daily oral dosage (mg)*	*Excretion*	*Biological half-life (h)*
ACE inhibitors			
Captopril	6.25 - 150	95% Renal	2 - 6
Enalapril	2.5 - 40	75% Renal	8 - 30
Quinapril	5 - 40	70% Renal	10 - 24
Lisinopril	5 - 10	70% Renal	18 - 30
Trindolapril	1 - 4	70% Hepatic	16 - 22
Perindopril	2 - 8	90% Renal	18 - 24
Fosinopril	10 - 40	50% Hepatic	12 - 30
Ramipril	2.5 - 10	70% Renal	24 - 60
AT receptor antagonists			
Losartan	50-100	85% Hepatic	2
Irbesartan	150 - 300	80% Hepatic	11
Candesartan	8 - 16	70% Hepatic	9
Telmisartan	40 - 80	80% Hepatic	20
Eprosartan	600 - 800	80% Hepatic	9

ACE inhibitors are indicated for hypertension, cardiac failure, to reduce the progression to symptomatic heart disease in patients with asymptomatic left ventricular dysfunction, to reduce remodeling in patients with myocardial infarction and reduced ejection fraction (particularly when therapy delayed for 2 days following the myocardial infarct),[98] reduction of cardiovascular mortality in patients with evidence of cardiovascular disease as well as nephropathy in diabetic patients[99] and decrease the progression of renal insufficiency in patients with chronic renal failure[100,101] (particularly diabetic and IgA nephropathy - an effect which is independent of their blood-pressure-lowering effect[92,102]).

ACE inhibitors are contraindicated during pregnancy (as they increase the incidence of foetal death, oligohydramnios and neonatal renal failure[103]) and in patients who have angio-oedema (causing oedema, hypotension, dyspnoea, or visceral pain), collagen vascular disease and bilateral renal artery or diffuse intrarenal vascular stenosis.

A persistent non-productive cough is a 'class' effect and one of the most troublesome side effects of ACE inhibitors. It develops in up to 25% of patients taking ACE inhibitors (particularly in patients of Chinese or African descent) and is thought to be due to an accumulation of bradykinin in lung tissue, stimulating C-fibre receptors and rapidly adapting stretch receptors (either directly or indirectly by increasing prostanoid sysnthesis[104]), both of which form part of the afferent limb of the cough reflex.[105] However, there is some evidence to suggest that the potentiation of the cough reflex is caused by an increase in substance P and neurokinin A formation (rather than bradykinin),[106] and may explain the reduced incidence of cough reported with fosinopril compared to enalapril.[107]

The cough generally resolves within a few days of stopping the ACE inhibitor and replacing it with another antihypertensive agent (e.g. the angiotensin-II-receptor antagonist, losartan). While some studies have suggested that it may be reduced by taking NSAID's, nifedipine or by inhaling sodium cromoglycate (2 puffs from a MDI 6-hourly, i.e. 40 mg daily),[108] these agents have not been universally successful. In one study of 9 patients with an enalapril induced cough, administration of the thromboxane antagonist (picotamide 600 mg orally twice daily), caused the cough to disappear within 72 hours in 8 patients.[109]

Angiotensin receptor blockers

Angiotensin receptor blockers (or antagonists) were first developed using angiotensin II analogues which directly competed with angiotensin II for tissue binding sites. However, these early peptide analogues had limited therapeutic potential. For example, the angiotensin II analogue saralasin required intravenous administration (i.e. had poor oral bioavailability), had a short half-life and demonstrated agonist activity in the presence of low angiotensin II levels. Recently, nonpeptide angiotensin II receptor antagonists have been developed (e.g. losartan, irbesartan, candesartan, telmisartan, valsartan and eprosartan, all of which are AT_1 receptor inhibitors, and PD123177 an AT_2 receptor inhibitor).[110-112]

When compared with ACE inhibitors, AT_1 receptor antagonism has the added advantages of preventing the effects of angiotensin II generated by non-ACE pathways, does not promote bradykinin activity (i.e. less cough and angio-oedema), and, as angiotensin II is under negative feedback control, inhibition of the AT_1 receptor increases renin release and angiotensin activation (i.e. there may be augmentation of non- AT_1 receptor actions of angiotensin, for example it may enhance the antiproliferative effects of AT_2 receptor stimulation).[113]

AT_1 receptor antagonism also causes less acute reduction of glomerular filtration rate than ACE inhibitors and have a renoprotective effect in hypertensive patients particularly those with type 2

diabetes[114] an effect that is beyond just a reduction in blood pressure[115,116] (however, it is not known yet if they reduce remodeling in patients with myocardial infarction and reduced ejection fraction,[117] particularly as the reduction in an experimental infarct size associated with the ACE inhibitor ramiprilat, was not shown with losartan[118]).

In one large prospective randomised trial of patients with primary hypertension and ECG evidence of left ventricular hypertrophy, losartan compared with atenolol (both up to 100 mg daily with the addition of hydrochlorathiazide 12.5 - 50 mg daily and if needed other antihypertensive therapy) was associated with a significant reduction in frequency of stroke (both had a similar incidence of myocardial infarction and cardiovascular mortality).[119] In another double-blind, randomised captopril-controlled trial of patients with heart failure and age > 65, losartan (beginning with 12.5 mg and titrated to 50 mg daily) was associated with a lower all-cause mortality, better tolerance, and no difference in renal dysfunction or hyperkalaemia when compared with captopril (beginning with 6.25 mg and titrated to 50 mg 8-hourly).[120] This effect may be due to a greater reduction of cardiac tissue noradrenaline at the neuroeffector junction with losartan compared to captopril (as production of non ACE angiotensin II and high bradykinin levels - both of which enhance the release of cardiac noradrenaline - occurs with captopril).[121]

Adrenergic receptor antagonists

Alpha adrenergic antagonists

Phenoxybenzamine. This is a selective non-competitive $alpha_1$ blocker which is 100 times more potent on $alpha_1$ than $alpha_2$ receptors.[122] Full alpha-blockade will be achieved when 100 mg of phenoxybenzamine is administered intravenously. This dose may be given over 1 h, with the blockade being complete 15 - 30 minutes after the completion of the intravenous dose, as metabolic transformation of phenoxybenzamine to an active metabolite is required first.

Phentolamine. This is a non selective competitive alpha-blocker, having equal affinity for both $alpha_1$ and $alpha_2$ receptors, which explains the tachycardia which may occur following the initial dose, due to the early $alpha_2$ receptor blockade.[122] For a continuous effect, phentolamine may be infused at 0.5 - 2 mg/min.

Chlorpromazine. This may also be used as a selective $alpha_1$ blocker, and an intravenous dose of 2.5 - 10 mg will produce hypotension for 1 - 2 h in patients with an increased sympathetic tone. Greater amounts than this seem to have no added effect.

Prazosin, doxazosin, tamsulosin and terazosin. These agents are selective $alpha_1$ blockers. While prazosin and doxazosin have been used as antihypertensive agents they have also been used to reduce dynamic obstruction associated with prostatic hyperplasia although tamsulosin and terazosin appear to be more beneficial in this condition than prazosin and doxazosin.[123]

The side effects of most of these agents include postural hypotension, nasal stuffiness, fluid retention, headache and drowsiness.

Beta adrenergic antagonists (i.e. beta blockers)

Beta-blockers are competitive inhibitors of the beta-adrenergic receptor, and have some or all of the characteristics of:

a. *Cardioselectivity*. Beta-blockers are classified as either non cardioselective (i.e. block both $beta_1$ and $beta_2$ receptors) or cardioselective (i.e. block the $beta_1$ receptor only). Most beta-adrenergic antagonists (including propranolol) do not block $beta_3$-receptor responses.
   i. Cardioselective drugs are selective in blocking the effects of cardiac stimulation, renin release and lipolysis (i.e. free fatty acid release) caused by adrenergic stimulation. By leaving the $beta_2$-receptors unblocked, cardioselective beta-blockers are considered to be safer to use in patients who have, acute or chronic obstructive pulmonary disease, intermittent claudication, chronic fatigue or diabetes mellitus requiring insulin. Severe hypoglycaemia stimulates adrenaline release, causing hepatic gluconeogenesis and glycogenolysis, tachycardia and tremor due to $beta_2$-receptor stimulation. Non selective beta-blockade suppresses the increase in blood glucose and block the clinical effects of hypoglycaemia, although it does not cause, or exacerbate, diabetes mellitus.[124] The cardio-selective drugs often exhibit selectivity at low dosage, with $beta_2$-receptor blockade occurring at a higher dose. Of the existing agents, the most selective agent appears to be atenolol, followed by metoprolol and then acebutolol.[125]
   ii. Noncardioselective drugs are theoretically desirable in the management of patients with hypertension, to block the presynaptic $beta_2$-receptor stimulation of noradrenaline release.
b. *Intrinsic sympathomimetic activity* (ISA). Pindolol, alprenolol and oxprenolol exert a partial agonist effect (i.e. ISA) as well as a beta-receptor blocking effect. These agents tend to have less effect on resting heart rate and cardiac output than agents without this property. There is some evidence that

agents with ISA are less likely to exacerbate Raynaud's phenomenon than the cardioselective agents and it appears that ISA may be more important in promoting skin blood flow than unblocked $beta_2$ activity.[124]

c. *Membrane stabilising activity (MSA)*. The MSA (i.e. local anaesthetic activity) of propranolol requires concentrations two to three orders of magnitude higher than those which provide beta-blockade; therefore, unless massive intoxication is present, the MSA is unlikely to be an important clinical effect of any beta-blocking drug.[124,126] Nevertheless, in patients with glaucoma, a beta-antagonist without MSA (e.g. timolol) is used to reduce any likelihood of decreasing the corneal reflex that can lead to corneal damage.

d. *Lipid solubility*. Propranolol, alprenolol, oxprenolol, and metoprolol are the most lipid soluble of the beta-blockers, whereas sotalol, esmolol and atenolol are the least lipid soluble. Pindolol occupies an intermediary position.[124] The more lipid soluble the drug is, the greater are its gastrointestinal absorption, 'first pass' effect (i.e. hepatic and gastrointestinal metabolism) and blood brain barrier permeability. Water-soluble beta-blockers tend to be eliminated by the kidney and tend to have longer half-lives.

e. *Other effects*. As well as a beta-blocking effect, carvedilol and labetalol have alpha-blocking effects,[127,128] and sotalol has the ability to prolong the QT interval.[129-131] The effect of sotalol on cardiac repolarisation occurs independently of its beta-blocking actions, because its dextro isomer (which has one-fiftieth the beta-blocking action of the levo compound), is equipotent with the levo isomer in prolonging the cardiac action potential.[129,130]
When adrenergic stimulation occurs in patients treated with beta-blockers, unopposed alpha-stimulation may increase afterload, reduce cardiac output and exacerbate cardiac failure.

f. *Indications*: beta-adrenergic blockers may be used to treat, hypertension, angina, post myocardial infarction, cardiac arrhythmias, migraine, obstructive cardiomyopathy, hyperthyroidism, glaucoma, anxiety, and autonomic overactivity associated with tetanus, porphyria, alcohol withdrawal and opiate withdrawal, and have been used to achieve hypotensive anaesthesia. Generally the beta-blocker chosen should be, cardioselective (i.e., $beta_1$ selective) and hydrophilic.[132] Beta-adrenergic blockers are contraindicated in patients who have complete heart block, severe bradycardia, cardiogenic shock, hypotension, congestive cardiac failure, acute and chronic obstructive pulmonary disease, severe depression, and Prinzmetal's angina. The latter may theoretically be exacerbated by unopposed alpha adrenergic receptor stimulation, thus calcium blockers should be used initially for this condition.

g. *Dosage*: the common oral and intravenous dose ranges,[133-135] are shown in table 6. Propranolol, oxprenolol, metoprolol and alprenolol all undergo a first-pass effect resulting in a 30 - 50% availability of the drug in comparison to an intravenous dose. Atenolol and sotalol do not undergo the 'first pass' effect, and while 100% of oral sotalol is absorbed only 50% of oral atenolol is absorbed. The intravenous dose of propranolol, metoprolol and atenolol usually exerts eight to 10 times the effect of an oral dose and is given at a rate of 1 mg/min up to 10 mg or until the desired effect is achieved.[136] Full beta-blockade should be achieved with an intravenous dose of 10-20 mg (i.e. 0.2 mg/kg) of propranolol.

Esmolol is a beta-blocking agent which is ultra short acting because it is rapidly metabolised by red blood cell esterases. It is cardioselective with an elimination half-life of 9.2 min and a duration of action of 10 - 30 min. Due to its short acting nature, it has certain therapeutic attractions relating to safety and control in the management of supraventricular tachycardias and hypertension . It is available in 10 mL glass ampoules containing 2.5 g. Two ampoules are diluted in 500 mL of 5% dextrose producing a concentration of 10 mg/mL. A loading dose of 500 μg/kg is infused over 1 min (35 mg/70 kg), followed by a progressively increasing rate at 4-minute intervals, beginning at 25 μg/kg/min (1.75 mg/70 kg/min), increasing by increments of 50 μg/kg/min (3.5 mg/70 kg/min) until the desired response is achieved. Dosages greater than 200 μg/kg/min (14 mg/70 kg/min) are usually not needed, although doses of up to 300 μg/kg/min (21 mg/70 kg/min) have been given safely.[137]

h. *Side-effects*: the side-effects of the beta-adrenergic blockers include fatigue, depression, gastrointestinal disturbances, pulmonary oedema, hypotension, heart block and rebound hypertension. Angina or myocardial infarction may occur in up to 5% of patients 12-48 h after acute withdrawal.[133,136] Sleep disturbances (e.g. nightmares) are associated with the lipid-soluble beta-blockers (e.g. propranolol, alprenolol, oxprenolol, pindolol, metoprolol) that penetrate the blood-brain barrier and may be reduced by treating with the water-soluble beta-blockers (e.g. atenolol or sotalol).

Table 6. Beta adrenergic blockers

Drug	*potency*	*IV mg/5 min*	*Oral mg/24h*	*Plasma half-life (h)*	*ISA*	*MSA*	*Excretion*
Nonselective ($beta_1$, $beta_2$)							
Propranolol	1	1 - 10	80 - 480	2 - 6		++	95% Hepatic
Alprenolol	0.5	5 - 20	200 - 800	1 - 3	++	+	95% Hepatic
Oxprenolol	1	1 - 10	80 - 640	1 - 2	++	+	95% Hepatic
Pindolol	6	0.2 - 1	10 - 30	4 - 5	+++	+	60% Hepatic
Sotalol	0.3	10 - 20	80 - 480	15 - 17			90% Renal
Cardioselective ($beta_1$)							
Atenolol	1	1 - 10	50 - 200	6 - 9			90% Renal
Metoprolol	1	1 - 10	50 - 400	3 - 6		$\pm$	95% Hepatic
Esmolol	0.07	50 - 300 (μg/kg/min)		9 min			95% Hepatic
Mixed ($beta_1$, $beta_2$, $alpha_1$)							
Labetalol	0.5	50 - 150	200 - 2400	3 - 4		+	95% Hepatic

ISA = intrinsic sympathomimetic activity, MSA = membrane stabilising activity

Calcium-channel blockers

Calcium-channel blockers act predominantly at the plasma membrane to block the slow current influx of Ca^{2+} during the plateau phase of the action potential. The slow inward current has a voltage-gated channel (with a voltage sensor) and a receptor-dependent channel. The voltage-gated channels are complex proteins made up of 4 - 5 subunits and are classified into L, N and T channels.[138] Calcium antagonists may be classified as non selective (e.g. halothane, isoflurane and enflurane have calcium-blocking effects.[139] Isoflurane appears to resemble nifedipine, while halothane and enflurane bear a closer relationship to verapamil and diltiazem[140]) and selective calcium-channel blockers.[141]

The selective calcium-channel blockers are chemically classified as the phenylalkylamines (e.g. verapamil), 1,4 dihydropyridines (nifedipine, felodipine, nicardipine, nimodipine, amlodipine) benzothiazepines (e.g diltiazem) and others (lidoflazine, bepridil).[139,142] The 1,4 dihydropyridpones prevent calcium entry by an extracellular modification of the voltage-dependent channel. The phenylalkylamines and benzothiazepines (which are ionised and water soluble), block the voltage-dependent channel in a frequency-dependent manner as they require the channel to be in the open or inactive state (i.e. when the channel is open to the ECF), to allow them to gain entry into the interior of the Ca channel before they can effectively block the channel.[143] Diltiazem and verapamil have a fast channel blocking capacity at high doses, nifedipine does not. All three drugs have specific binding sites within the channel although they all bind to the α_{1c} subunit of the voltage-dependent L-type calcium channel (i.e. the major pore forming unit of the channel).[144] They are used for one or more of their cardiovascular effects of inhibition of conduction, chronotropism and refractoriness (particularly at the SA and AV nodes), to treat supraventricular tachycardias, negative inotropism, to treat hypertrophic subaortic stenosis and variant angina, and arteriolar vasodilation to treat hypertension[145] and cerebral vasospasm.

However, selective calcium-channel-blockers may increase rather than decrease mortality in certain situations. For example, hypertensive patients treated with calcium-channel blockers (particularly high doses of the shorter acting dihydropyridine class, e.g. nifedipine, felodipine, nicardipine, isradipine), may have an increased risk of myocardial infarction and an increase in mortality[146-148] (although, another study did not confirm this[149]), also patients with coronary artery disease[150] or heart failure[151] who are treated with nifedipine appear to have a dose related increase in mortality, an increased risk of perioperative bleeding[152] or gastrointestinal haemorrhage[153] (due to an inhibition of platelet aggregation, particularly in elderly patients) and perhaps even an increased incidence of cancer (due to inhibition of cell apoptosis,[154] although a recent review of all the evidence does not support the latter[155]). Diabetic patients are a subgroup who are particularly vulnerable to an increased cardiovascular complication rate with calcium-agonist therapy.[144] Verapamil and amlodipine appear to be the safest calcium channel blockers to use in patients with acute ischaemic heart disease.[156]

Verapamil is a papaverine derivative and a racemic mixture of equal amounts of dextro (D) and levo (L) isomers. While it is often used to terminate or control the rate of supraventricular tachycardias, it has also been used to treat hypertension, particularly when beta blockers are contraindicated (e.g. in patients with obstructive airways disease).[157] The oral dose ranges from 40-120 mg 8-hourly, to a maximum dose of 720 mg/day. The onset, peak and duration of action are 1, 2 and 4-6 h, respectively

Verapamil is subjected to extensive first-pass hepatic extraction resulting in an oral bioavailability of only 10-20%, thus an equivalent oral dose is 8 - 10 times the intravenous dose. Verapamil is 90% protein bound, has a half-life 3 - 7 h and is 95% metabolised by the liver. The side-effects include, hypotension, bradycardia, severe constipation (occurring in 30-40%, and may be corrected with 1.36 mmol of intravenous calcium[158]), gastrointestinal haemorrhage, fatigue, headache, dizziness, fluid retention and, rarely, galactorrhoea and hepatotoxicity.[159]

Diltiazem is often used to terminate or control the rate of supraventricular tachycardias although like verapamil it has also been used to treat hypertension. The oral dose ranges from 30 to 90 mg 6-hourly. The onset, peak and duration of action are 15 min, 30 min and 4 h, respectively. It has an oral bioavailability of 24% (which increases to 90% after continued oral intake due to an alteration in first-pass effect) and is 80% protein bound.

The side-effects include headache, dizziness, flushing, hypotension and rarely gastrointestinal haemorrhage. It seems not have the severe constipating or alteration in digoxin excretion side-effects which are often associated with verapamil.

Nifedipine is not frequency dependent and may act by 'plugging' the outer opening of the calcium channel. It has minimal cardiac effects at the dosages employed. For example, the dose required to impair AV nodal conduction appear to be about 10 times the amount required for coronary vasodilation. While nifedipine has a powerful negative inotropic action in vitro it does not appear to depress cardiac output in vitro, probably due to its vasodilation properties reducing afterload and the associated reflex sympathetic stimulation increasing cardiac inotropism and rate.[157] The oral dose ranges from 30 to 120 mg/day. Sublingual absorption is almost complete (bypassing hepatic first-pass effect). First-pass hepatic extraction is not as high as for verapamil with 65% of the drug being bioavailable; 90-98% of the drug is protein bound to albumin. The side-effects include headache (6%), hypotension, flushing, dizziness, palpitations, tachycardia, fluid retention and, rarely, gingival hyperplasia and joint pain. Angina at rest (30 min after an oral dose) and worsening of cerebral ischaemia have also been reported, and a vascular steal has been the suggested mechanism.[160]

Felodipine is a calcium antagonist which has, in comparison with nifedipine or verapamil, a greater selectively for vascular smooth muscle (i.e. 100 times) than myocardial muscle. When given acutely it may reduce the peripheral resistance by up to 40%. The oral dose ranges from 2.5 to 10 mg 12-hourly, or once a day with an extended release formulation. Felodipine is well absorbed from the gastrointestinal tract, although undergoes an extensive first-pass metabolism, resulting in a 15% bioavailability.[161] The side-effects include peripheral oedema, headache, flushing, palpitations (due to a reflex tachycardia), dizziness, dyspnoea, muscle pain and fatigue, requiring withdrawal of therapy in about 7% of patients. As with nifedipine, gingival hyperplasia, aggravation of angina, chest pain and myocardial infarction have been reported.

Amlodipine is a calcium-channel blocker of the dihydropyridine class which is selective for vascular smooth muscle.[162,163] Unlike nifedipine it has a gradual onset antihypertensive effect (a single dose reduces the blood pressure gradually over 4 to 8 hours and returns to the baseline after 1-3 days) and, unlike other calcium-channel blockers, amlodipine appears to have antiatherosclerotic, antithrombotic and antihypertropic actions.

The oral dose ranges from 2.5 to 10 mg daily. Amlodipine is almost completely absorbed from the gastrointestinal tract and has a relative high bioavailability of 60% to 80% which is not altered by food. Peak plasma concentrations occur in 6 - 12 hours. It has an elimination half-life of 40 hours, thus it reaches a steady state with daily administration after one week, so the dose should be changed no sooner than once every 7 days. Amlodipine is more than 95% is plasma protein bound. The side-effects include peripheral oedema, headache, flushing, muscle cramps, frequency of micturition, nocturia, coughing, impotence, asthma, epistaxis, agitation and conjunctivitis. Unlike nifedipine it rarely causes postural hypotension or reflex tachycardia.

Dopamine$_1$-receptor (DA_1) agonists

Intravenous fenoldopam mesylate (a selective dopamine$_1$-receptor (DA_1) agonist that acts as a peripheral arteriolar vasodilator and also has a mild diuretic action) at 0.1 - 1.6 μg/kg/min has been used successfully to manage patients with acute hypertension. It has no activity as an agonist on dopamine$_2$-receptor (DA_2) or alpha- or beta-adrenergic receptors,[164] although a reflex tachycardia may occur when the agent is used intravenously.

It has an onset of action of 5 - 10 min, which peaks after 15 - 30 min and lasts for 15 - 30 min. It has an elimination half-life of 10 minutes and the side-effects of fenoldopam include, headache, flushing, dizziness, tachycardia, bradycardia, T wave inversion, increase in intraocular pressure.

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