REVIEW ARTICLE

Drugs 2007; 67 (14): 2023-2044
0012-6667/07/0014-2023/$49.95/0

Drugs for the Perioperative Control of Hypertension

Current Issues and Future Directions

Robert Feneck

Department of Anaesthesia, Guys and St Thomas' Hospitals, London, England

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Abstract

The management of hypertension continues to pose important challenges. Recent developments have established the importance of more rigorous blood pressure control in the community. In the perioperative setting, hypertension has long been recognised as undesirable, although the adverse impact of high blood pressure on the acute risks of elective surgery may have been previously overstated.

A number of agents and techniques are available to control blood pressure perioperatively. These include principally general and regional anaesthetics, α_2-adrenoceptor agonists, peripheral α_1- and β-adrenoceptor antagonists, dihydropyridine calcium channel antagonists, dopamine D_{1A}-receptor agonists (fenoldopam), and nitric oxide donors.

Recent years have seen important developments in the receptor selectivity of new compounds and in pharmacokinetics, particularly esterase metabolism. The

future study of genomics may enable us to identify patients at risk for hypertension-related adverse events and target therapies most effectively to these high-risk groups.

Haemodynamic control is an essential component of safe perioperative care. The importance of hypertension in the perioperative period has long been recognised and early recommendations for the anaesthetic management of hypertensive patients date from >30 years ago.[1-3] These early studies, constantly reaffirmed in our current daily clinical practice, suggest that in susceptible patients, sympatho-adrenal activation and perioperative hypertension may lead to adverse effects, including myocardial ischaemia and haemorrhage. These adverse events are themselves linked to poor outcomes, yet they can be prevented by good cardiovascular control.

Thus, our understanding of a patient's needs in the perioperative period is even greater today, and fortunately we have numerous drugs and techniques available to deal with them. Good haemodynamic control needs to be achieved throughout the perioperative period, and not surprisingly, successful management in the pre-operative period is often the key to success. However, there are other important factors that may have an impact even in those patients who were normotensive before surgery. Furthermore, if we are to achieve control of blood pressure throughout the perioperative period, we need to be clear about the mechanisms of hypertension so that we can choose the best agents and techniques to address the problem.

This article reviews the current issues related to perioperative hypertension, including the causes and effects of hypertension, the preoperative management of hypertensive patients and the risks involved in anaesthetising patients with high blood pressure preoperatively. Information is given about the available agents for perioperative management, and the role of genomics in identifying those patients at risk and those likely to respond to therapy is explored.

Information for this article was obtained from a number of sources. Evidence-based recommendations were obtained via a literature search from 1970 to 2007 using MEDLINE and the Cochrane Database. Prominence was given to information from randomised controlled trials, meta-analyses of randomised controlled trials and authoritative observational databases, as well as informed consensus opinion from authoritative guidelines. However, other data and opinion from standard texts have been included where it is felt to be both instructive and of interest. Pharmacological information was obtained from randomised controlled trials, meta-analysis and review articles and consensus guidelines, as well as standard texts.

1. Current Issues

1.1 Blood Pressure Control Patients with Pre-Existing Hypertension

The current classification of hypertension as recommended by the Joint National Committee for Hypertension is shown in table I.[4] There are a number of features in the classification of hypertension that have changed in recent years. For example:

- in individuals aged >50 years, systolic blood pressure (SBP) of >140mm Hg is a much more important cardiovascular disease risk factor than diastolic blood pressure (DBP);
- the risk of cardiovascular disease, beginning at 115/75mm Hg, doubles with each increment of 20/10mm Hg;

Table I. Classification of blood pressure for adults[4]

Classification	SBP (mm Hg)	DBP (mm Hg)
Normal	<120	and <80
Pre-hypertension	120–139	or 80–89
Stage 1 hypertension	140–159	or 90–99
Stage 2 hypertension	>160	or >100

DBP = diastolic blood pressure; **SBP** = systolic blood pressure.

- individuals who are normotensive at 55 years of age have a 90% lifetime risk for developing hypertension;
- individuals with a SBP of 120–139mm Hg or a DBP of 80–89mm Hg should be considered as pre-hypertensive and require health-promoting lifestyle modifications to prevent cardiovascular disease.

Recommendations were also made for the institution of antihypertensive therapy. Although these are not the subject of this article, the tighter control inherent in the new requirements and the treatment recommendations will result in more patients taking antihypertensive therapy when presenting in the perioperative setting.

Thus, target blood pressures for patients in the community have been set that are significantly lower than previously recommended,[4] and these targets have been validated by observed reductions in the morbidity and mortality from hypertensive disease in the community.[5] It is not clear whether the achievement of such lower values will significantly affect the risk either of developing perioperative hypertension or more importantly reduce those adverse outcomes associated with it.

1.2 Effects of Hypertension

The causative mechanism for hypertension remains poorly understood. No single or specific cause is usually found in up to 95% of patients presenting with significantly raised blood pressure. Thus, primary or essential hypertension may result from a complex interaction of renal, neurogenic, endocrine and cardiovascular factors, particularly alterations in the activity of the vascular endothelium. Many of these may be influenced by genetic variability.

A number of specific conditions may also be responsible:

- chronic kidney disease;
- coarctation of the aorta;
- Cushings syndrome and other glucocorticoid excess states including long-term corticosteroid therapy;
- drug induced or drug related;
- obstructive uropathy;
- phaeochromocytoma;
- primary aldosteronism and other mineralocorticoid excess states;
- renovascular hypertension;
- sleep apnoea;
- thyroid or parathyroid disease.

These causes of secondary hypertension are important since they may have implications for other aspects of perioperative care.

Of much greater importance are the effects of hypertension, particularly when long standing, and the association of other conditions that may precipitate significant problems in the perioperative period.

Clearly, renal disease may be associated both with the development of high blood pressure and adverse effects resulting from established hypertension. Long-standing hypertension has been associated with an increased incidence of renal dysfunction, and numerous studies have identified renal dysfunction as a determinant for cardiovascular morbidity and mortality,[6,7] and an outcome determinant for patients undergoing cardiac[8-10] and non-cardiac surgery.[11-13]

Hypertension has a significant adverse effect on the autoregulation of blood flow in many vascular beds including the cerebral circulation, where the curve is shifted to the right. As a result, a fall in blood pressure may result in a reduction in cerebral blood greater than would be seen in normotensive individuals.[14]

Hypertension represents a significant increase in left ventricular afterload, which may lead to left ventricular hypertrophy and, in due course, to left ventricular dilatation and failure.[15] The association between hypertension and the development of coronary artery disease is well documented, and the association between coronary artery disease and adverse perioperative outcomes has been similarly extensively documented.[16-18]

1.3 Significance of Perioperative Hypertension

Those patients with significantly raised blood pressure preoperatively will be more likely to need

blood pressure control in the intraoperative and postoperative period.[19] In cardiac surgery, even isolated systolic hypertension has been shown to be associated with adverse outcomes,[20] including an increased risk of bleeding and blood transfusion.[21]

For others, does perioperative hypertension really matter? That is, do isolated perioperative readings of blood pressure even to the level of stage 3 hypertension require acute treatment with antihypertensive drugs?

The association between hypertension and adverse outcomes from surgery has been the subject of numerous studies. Early studies noted that anaesthesia in the patient with poorly controlled hypertension was associated with an increase in haemodynamic lability and an increased risk of myocardial ischaemia, and thus noted that "untreated high arterial pressure constitutes a serious risk to patients undergoing anaesthesia and surgery", and concluded that symptom-free patients with high initial arterial pressures who are exposed to anaesthesia should be started on antihypertensive therapy.[1] Later studies failed to establish that pre-existing hypertension was a major preoperative cardiac risk factor unless the DBP exceeded 110mm Hg.[22-25] More recently, a large systematic review and meta-analysis concluded that there is little evidence for an association between admission arterial pressures of <180mm Hg systolic or <110mm Hg diastolic and perioperative complications.[26] Although there is little evidence that isolated systolic hypertension is a risk factor in non-cardiac surgery, it frequently occurs in the adult population, and 'white-coat hypertension' is more common amongst females and accounts for a high proportion of abnormal blood pressure measurements in the clinic.[27,28] Using a conservative definition of white-coat hypertension, observations suggest that the rate of cardiovascular events in white-coat hypertension is little different to that seen in normotensive individuals, but that when a more liberal definition and higher ambulatory pressure is selected, adverse event rates increase.[29] There are few data on the incidence of white-coat hypertension in the perioperative setting.

The guidelines issued by the American College of Cardiology/American Heart Association (ACC/AHA) on perioperative cardiac risk and hypertension suggest that a SBP of <180mm Hg and DBP of <110mm Hg is not an independent risk necessitating control before, and hence delay of, surgery. However, they suggest that patients with pressures above these levels should have them controlled before surgery, when necessary rapid control may be achieved intravenously and that β-adrenoceptor antagonists (β-blockers) are attractive drugs for this purpose.[30]

Others have suggested that the evidence for delaying surgery in uncomplicated hypertension even to the level of stage 3 (>180/110mm Hg) is weak,[26,31,32] particularly if there is no evidence of end-organ damage.

More complex conditions associated with moderate hypertension have not yet been comprehensively evaluated. For example, the association between the metabolic syndrome (hyperlipdaemia, central adiposity, diabetes mellitus and hypertension) in the absence of symptoms of coronary artery or cerebrovascular disease and adverse perioperative outcomes has not been clearly evaluated, although patients with this condition undergoing surgery may pose a number of problems for physicians perioperatively.[33]

Thus, we can conclude that elective surgery need not be delayed in patients with a SBP of <180mm Hg and a DBP of <110mm Hg, but that readings greater than these levels should be cause for caution and concern. Pre-operative control may be wise, particularly if there is evidence of end-organ damage, and enhanced monitoring, for example, intra-arterial blood pressure monitoring may be necessary to guard against the development of intraoperative haemodynamic lability. The patient's blood pressure should be kept within 20% of the baseline value;[26,30] this value itself may be considered excessive in certain types of surgery, further suggesting the value of delaying surgery to achieve preoperative blood pressure control.

Even so, perioperative hypertension should not be ignored. Elevated blood pressure readings

Table II. Commonly used drugs for perioperative blood pressure (BP) control

Drug	Onset (min)	Dose	Comments
Esmolol	1–2	500 μg/kg/min for 4 min, then 150–200 μg/kg/min IV	Ultrashort-acting cardioselective β-adrenoceptor antagonist
Metoprolol	2–3	1–5mg IV	Cardioselective β-adrenoceptor antagonist
Labetalol	3–6	20mg IV bolus every 5 min, repeated as required or infusion 2 mg/min	α- and β-adrenoceptor antagonist
Propranolol	3–5	1mg IV	Non-cardioselective β-adrenoceptor antagonist. CNS penetration
Atenolol	5	5mg IV repeated	Cardioselective β-adrenoceptor antagonist. Long acting
Nifedipine	8–12	1.5–3 μg/kg/min	Dihydropyridine calcium channel antagonist
Nicardipine	5–10	5–15 mg/h IV in 70kg adult	Dihydropyridine calcium channel antagonist
Isradipine	5–10	0.5–1.0 μg/kg/min	Dihydropyridine calcium channel antagonist
Fenoldopam	3–6	0.03–0.1 μg/kg/min	Synthetic selective dopamine receptor agonist
Sodium nitroprusside	<1	1–2 μg/kg/min IV	Cyanide toxicity if dosage excessive
Glyceryl trinitrate	2–5	10–50 μg/min IV	Bolus may be needed initially to control BP
Hydralazine	5–1	2.5–5.0mg IV	Long acting

IV = intravenous.

throughout the perioperative period should be carefully evaluated taking into account the patient's usual resting blood pressure, the duration and severity of the hypertension, the nature of the surgery and, in particular, the risks of postoperative haemorrhage, the patient's status regarding other cardiovascular risk factors, and the presence of other precipitating factors including pain and anxiety. Failure to take note of these criteria may lead to the excessive use of antihypertensive drugs, possible adverse or untoward effects from such drugs or over-active control of blood pressure leading to reductions in vital organ perfusion.

2. Antihypertensive Drugs

2.1 General Measures

Those patients who are treated for pre-existing hypertension will be taking a variety of drugs that have important effects in the anaesthetised patient. Those managing the patient may be able to make use of these effects to facilitate their perioperative care. The importance of general measures in controlling perioperative hypertension cannot be overstated. Hypertension occurring during surgery is most properly managed by attention to the adequacy of analgesia and anaesthesia. The antihypertensive effects of modern volatile anaesthetics are frequently used first to control blood pressure before any specific therapy is given.[19] In the perioperative period, hypoxia and hypercapnia may be associated with sympathoadrenal activation and high blood pressure may result. This should be excluded or treated appropriately before specific antihypertensive therapy is given. Similar considerations should be given to perioperative pain and anxiety. In patients receiving analgesia via the epidural route, additional top up may be particularly successful in resolving both pain and elevated blood pressure.

The drugs commonly used for perioperative blood pressure control are listed in table II and the properties of the ideal drug for the purpose are listed below:

- easy to prepare, stable at ambient temperature and light;
- given by continuous intravenous infusion;
- compatible with a range of diluents;
- easily titratable, with rapid onset and short duration of action;
- free of untoward or undesirable effects;
- other non-cardiovascular effects should be desirable and have a ceiling;

- free of effects on intracardiac conduction;
- mild reduction in myocardial contractility;
- vasodilator effects should be mostly confined to the arteriolar bed (i.e. resistance vessels);
- vasodilator effects preferentially in vital organ vascular beds, e.g. coronary, renal splanchnic;
- effective treatment should maximise protective effects against complications of hypertension, i.e. myocardial ischaemia.

Many of the desirable features listed are self-explanatory. Chemical stability and compatibility are obviously desirable. The intravenous route is preferable since bioavailability is 100% and the onset of action is quicker than by other routes. Adverse and toxic effects should be at a minimum. Many of the drugs discussed in this section meet some of the desirable criteria listed above but none meet them all.

In perioperative hypertension, therapy should be directed towards correcting the physiological abnormality. This is most frequently related to sympathoadrenal activation, resulting in an increase in resting arteriolar tone, venoconstriction with reduced pooling of venous blood, and an enhanced inotropic state. Logically, appropriate therapy would result in arteriolar dilatation, a mild reduction in venous tone and a mild to moderate reduction in contractility.

The availability of suitable drugs may also vary between different countries. A comprehensive list of drugs is available from numerous standard texts on pharmacology. Those agents and techniques that are currently of interest and widely, though not universally, available are discussed in sections 2.2–2.6.

2.2 α_2-Adrenoceptor Agonists/Imidazole Receptor Agonists

α_2-Adrenoceptor agonists possess properties of sedation, analgesia and blood pressure control, which may be relevant to the period before, during and after surgery.

Adrenoceptors have been the subject of extensive study since Ahlquist's classification into α- and β-receptors in 1948.[34] Lands et al.[35] and Langer[36] have since identified the α- and β-subtypes, and further subfamilies of α-adrenoceptors have been identified including three α-adrenoceptor subtypes in mammals, but as many as 14 subtypes in other species, such as the pufferfish.[37]

Adrenoceptors are seven-stranded G-protein-linked cell membrane receptors, of between 415 and 480 amino acids in length.[38] Ligand binding studies suggest that the fourth domain of the seven-stranded α_2-adrenoceptor is linked to the ligand.[39] α_2-Adrenoceptors are linked to Gi protein, thus activation of the α_2-adrenoceptor in the CNS will cause activation of Gi protein, which will inhibit adenylyl cyclase leading to a reduction in the generation of cyclic 3′5′ cyclic adenosine monophosphate (cAMP). However, the activated α-adrenoceptors also produces its effects by other mechanisms including decrease in calcium entry into nerve channels, a reduction in phosphatidyl inositol metabolism and possibly by inhibition of ganglionic transmission.[40] Activated Gi proteins may also activate a variety of ion channels including potassium channels in the cell membrane.[41]

α_2-Adrenoceptors in the CNS appear to be primarily situated in the loecus coerulus located bilaterally in the floor of the fourth ventral.[42] This site has afferent connections to the rostral ventrolateral medullary nuclei, and efferent connections to noradrenergic fibres that connect to the thalamus and elsewhere. In addition, high densities of α_2-adrenoceptors have been shown to be present in human intermediolateral cell columns and the substantia gelatinosa.

Early experimental work revealed that in contrast to the catecholamines, imidazoline compounds produced hypotension following direct intramedullary injection. These observations led to the proposal of non-adrenergic receptors specifically recognising imidazoline-like compounds located in the reticularis lateralis of the ventrolateral medulla. Two types of imidazoline receptors have since been identified (i) imidazoline I_1-receptors located in the brain; and (ii) I_2-receptors located in brain, pancreas and kidney.[43] Many α_2-adrenoceptor agonists have activity at I_1-receptors. I_1-receptor activity appears to be associated with centrally mediated vasodilation and hypotension.[44] Although not fully eluci-

dated, it appears that I_1-receptor agonists mediate their effects through a G-protein-linked mechanism resulting in an increase in arachidonic acid and the subsequent release of prostacyclins.

Recent developments of I_1-receptor agonists with a reduced level of α_2-adrenoceptors have resulted in drugs with a cleaner haemodynamic profile. Moxonidine[45] and rilmenidine[46] are the prototypes of this new class of centrally acting antihypertensives. Both drugs have a much weaker affinity for central α-adrenoceptors than clonidine and methyldopa, and the adverse-effects profile of the I_1-receptor agonists is significantly better.

Clonidine has since been shown to reduce the minimal alveolar concentrations of anaesthetic drugs.[47-49] Dexmedetomidine has also been shown to be effective in reducing minimum alveolar concentration (MAC),[50,51] and may be an anaesthetic in its own right, suggesting a more complex mechanism of action.

The cardiovascular effects of α_2-adrenoceptor agonists are typified by clonidine and are best described as a biphasic response. At lower doses, the predominant effect is sympatholysis mediated by agonist activity at the α_2-adrenoceptor. At higher doses, a peripherally mediated hypertensive effect is seen as a result of activation of α_{2B}-adrenoceptors, thought to be located on smooth muscle cells in arteriolar vessels. This biphasic effect may be demonstrated in the initial dose administration stage of treating patients with α_2-adrenoceptor agonists, as a result of early short-acting peripherally mediated vasoconstriction preceding a long-lasting centrally mediated antihypertensive effect.[40]

Although clonidine clearly has blood pressure lowering properties, the majority of clinical studies that highlight its cardiovascular effects are concerned with sympatholytic effects rather than simple blood pressure lowering. Clonidine has been shown to improve circulatory stability including heart rate control and baroreflex activity.[52] Despite early studies questioning the benefit of prophylactic sympatholysis with clonidine, more recent data have suggested that perioperative administration of clonidine to patients at risk for coronary artery disease significantly reduces the incidence of perioperative myocardial ischaemia and postoperative death.[53-56]

Dexmedetomidine is an isomer of medetomidine, and has greater selectivity and specificity for α_2-adrenoceptors than clonidine.[57] It produces clinically significant effects at plasma concentrations of <1.0 ng/mL and has complex pharmacokinetics, which are concentration-dependent but non-linear. It has been extensively studied in humans, particularly in the setting of sedation in the intensive-care unit (ICU).[58-60] In this setting, its properties of providing sedation, analgesia without respiratory depression (albeit with a clear ceiling effect) and sympatholysis with effective blood pressure control would appear to be highly desirable. Dexmedetomidine in the ICU or post-anaesthesia-care unit is associated with a mild reduction in blood pressure, such as would be required for good haemodynamic control following surgery, and studies before and after surgery suggest a blood pressure controlling effect.[61,62] Intravenous administration should be undertaken with care as the biphasic effect on blood pressure may be seen, but most studies have shown this to be a manageable and transient effect. However, there are no data yet to suggest that α_2-adrenoceptor agonists in general, or dexmedetomidine in particular, would be useful for the rapid control of blood pressure required for the management of perioperative hypertension.

Mivazerol is an imidazoline compound that has been studied primarily in the setting of perioperative sympatholysis. There have been no studies designed to evaluate the place of mivazerol in the setting of perioperative hypertension. However, in common with other α_2-adrenoceptor agonists, mivazerol has been shown to be useful as a sympatholytic in patients undergoing high-risk surgery.[63-65]

Thus α_2-adrenoceptor agonists, particularly those with I_1-receptor activity, provide a highly desirable 'package' of effects (analgesia, sedation and sympatholysis) and should feature prominently in future protocols for perioperative blood pressure control. However, their effectiveness at controlling acute severe systemic hypertension has not been studied and, given the biphasic effect on blood pres-

sure seen, it may be that other agents will be preferable for this purpose.

2.3 Antihypertensive Drugs that Act at the Spinal Cord

Local anaesthetics, μ-opioid receptor agonists and α_2-adrenoceptor agonists have all been used in spinal techniques. Local anaesthetics may directly reduce vascular tone when given by the intrathecal or epidural route as a result of their effect in blocking nerve impulses in the sympathetic chain.

The sympathetic trunk receives preganglionic fibres from T1–T12. These are lightly myelinated B fibres and hence are more easily blocked than the larger heavily myelinated A fibres involved in sensory and motor transmission. One practical result is that sympathetic blockade is usually more extensive and, in particular higher, than sensory or motor block.

An epidural block to the level of T6 or above will produce vasodilatation and a reduction in peripheral resistance. A block up to the level of T2 may block cardiac accelerator nerves producing both vasodilatation and bradycardia. Under these circumstances, vasodilatation may be severe. Reduction in venous tone and hence venous return may also significantly reduce cardiac output.

The drugs that are commonly used for spinal techniques are bupivacaine, levobupivacaine and ropivacaine. Their pharmacology has been extensively described elsewhere.[66]

Spinal, and particularly epidural techniques, are widely used in the perioperative period both for intraoperative and postoperative pain control, with the additional benefit of providing control of blood pressure through sympathetic blockade. When the block is extensive, widespread vasodilation and bradycardia may produce an adverse combination of low blood pressure and low cardiac output. Thus, it is commonplace to preload the circulation with intravenous fluids and to have peripherally acting vasopressors available for immediate use.

The rapid and occasionally unpredictable onset of hypotension has meant that spinal anaesthetic techniques are rarely used as a means of controlling acute severe hypertension. Rather, they are used in the perioperative period in order to provide analgesia and circulatory control, as part of a package in a manner similar to that provided by the α_2-adrenoceptor agonists, and many have commented on their value.[67-69] However, there are clinical and organisational issues that may make them less attractive. Epidurals are obviously more invasive, and their safe use in the hypertensive vasoconstricted patient is more challenging. Inadvertent spinal anaesthesia is a rare, but serious, complication and despite published successes,[70,71] many institutions still insist on managing patients with indwelling epidural catheters in a more highly staffed area for safety reasons. This either limits their duration of effective use or significantly increases the resources necessary for their prolonged postoperative use.

Although there have been numerous studies comparing epidural, spinal and general anaesthetic techniques in a variety of surgical settings, most studies have looked at a number of aspects rather than concentrate on cardiovascular control. Most individual studies have been inadequately powered for cardiovascular safety analyses. A recent meta-analysis suggesting a beneficial effect of neuroaxial blockade[72] has been challenged[26,73] and the current situation is still somewhat confused.

2.4 Drugs that Act at Peripheral Receptors

2.4.1 α-Adrenoceptor Antagonists

Adrenergic α- and β-receptors are all seven-stranded G-protein-linked receptors, which, when activated, result in a conformation change in the G-protein complex leading to activation of second messengers. The G-protein linkage with adrenoceptors varies according to subtype. Compared with α_2-adrenoceptors, the α_1-adrenoceptor is linked to Gq protein. Ligands or drugs binding to this receptor produce activation of Gq proteins, which in turn leads to activation of phospholipase C and the conversion of phosphoinositol diphosphate to diacyl glycerol and inositol triphosphate, which leads in turn to an increase in intracellular calcium within smooth muscle cells, leading to vasoconstriction.[74]

Thus α_1-adrenoceptor antagonists will inhibit this process, leading to vasodilatation.

α_1-Adrenoceptor antagonists can be divided into selective (doxazosin, indoramin, prazosin, terazosin) and non-selective (phentolamine, phenoxybenzamine) compounds. For acute perioperative blood pressure control, these drugs have their limitations. Only phentolamine and phenoxybenzamine are available for intravenous injection, and although prazosin is certainly effective when given orally, the lack of an injectable preparation has obvious disadvantages.

Phenoxybenzamine combines irreversibly with the α_1-adrenoceptor and thus has a profoundly long duration of action. Its use has been described in the setting of resistant severe hypertension, especially associated with phaeocromocytoma and usually in combination with a β-blocker.[75-77]

Phentolamine has also been used in the setting of phaeochromocytoma,[77] but is usually used as a short-term treatment for perioperative vasoconstriction and hypertension. Tachyphylaxis, reflex tachycardia and increased circulating noradrenaline (norepinephrine) levels make it difficult to use for prolonged blood pressure control in the perioperative period, but it is commonly used as a vasodilator in special circumstances such as cardiopulmonary bypass, where the effects mentioned in the previous paragraph have less of an impact. Although the effective dose may be very variable, it is rare to need more than 1mg intravenously at a time, although repeated administration may be necessary.

2.4.2 β-Adrenoceptor Antagonists (β-Blockers)

β-Blockers are used in the perioperative setting in the manner described in the following subsections.

As a Continuation of Existing Antihypertensive Therapy

Despite their widespread clinical application, the antihypertensive mechanism of action of long-term β-blocker therapy is not fully understood. Previously, β-blockers were considered essential first-line drugs in the management of hypertension in the community, but recent data have thrown this into question and highlighted the value of calcium channel blockade and ACE inhibition as an alternatives.[78-80]

However, patients taking β-blockers long term should not have these withdrawn before surgery,[81] and continued use of β-blockers may have beneficial effects on the incidence of perioperative hypertension,[82-84] as well as atrial fibrillation,[85-87] and adverse myocardial outcomes.[83-87] Recent guidelines suggest that β-blockers should be continued in patients who are receiving such therapy to treat angina, arrhythmias, hypertension or other ACC/AHA Class I guideline indications.[30]

As a Prophylactic Treatment to Reduce Perioperative Complications

The perioperative use of prophylactic β-blockers has been the subject of much research and controversy. However, this has been concerned with their role in limiting adverse cardiovascular events, including arrhythmia,[85-87] adverse neurological events,[88] and adverse myocardial outcomes including perioperative myocardial ischaemia and infarction, in patients at risk from these events.[89-97] However, despite the significant amount of evidence and opinion supportive of their use, some questions remain. The reliability of the evidence in favour has been questioned[98,99] and others have noted that while β-blockers may reduce adverse events in the highest risk patients, those patients at reduced risk receive no benefit and may even experience worse outcomes than controls.[93] The importance of tight heart rate control has been convincingly advocated[100,101] as has the use of longer-acting β-blockers to ensure effective cover during the perioperative period.[102] Although guidelines recommend perioperative β-blockade most strongly in patients undergoing vascular surgery, other patients at high cardiac risk and undergoing intermediate- or high-risk procedures receive qualified support for β-blockade.[103] A recent meta-analysis suggests only limited benefit in patients undergoing either cardiac or non-cardiac surgery.[104]

Most authorities agree that some patients will show some benefit from perioperative β-blockade, but which patients, which β-blocker, administered for how long and producing what level of clinical

benefit are all questions that the current literature is not yet able to fully resolve.[105-107] The relationship between any such benefit and the presence of pre-existing hypertension with and without organ damage is not clear.

As Treatment for Hypertension in the Perioperative Period

The role of β-blockers as active treatment for perioperative hypertension is both well established and relatively straightforward. β_1-Blockers will reduce heart rate and contractile power and, therefore, tend to reduce blood pressure. The choice of β-blocker is likely to be guided by pharmacokinetic considerations including the speed of onset, duration of action and the presence of effects other than β_1-adrenoceptor antagonism. β_2-Blocker activity may provoke adverse effects including bronchospasm, which, in a patient either during surgery or recovering from anaesthesia, are potentially hazardous. CNS penetration, a recognised feature of propanolol, is unlikely to be useful since sedation and anxiolysis may be provided by other means. However, activity at other receptors may be highly desirable and labetalol, a drug combining α- and β-receptor antagonist activity, has proved extremely useful in the management of perioperative hypertension.[108-110]

Pharmacokinetic considerations may significantly influence the choice of agent. Despite the continued use of propranolol in some quarters, esmolol, metoprolol, atenolol and labetalol are the most commonly used intravenous β-blockers for perioperative β-blockade for blood pressure control.

Esmolol is 60% protein bound and undergoes renal excretion. It has a half life of ≈9 minutes because of its rapid metabolism by esterase hydrolysis.[111] As a result, esmolol has been used in the management of acute hypertensive events at induction and endotracheal intubation,[112,113] during surgery,[114,115] during emergence and endotracheal extubation,[116,117] and during the postoperative period both as prophylaxis and as therapy.

Metoprolol is a cardioselective compound and thus carries a substantially reduced risk of adverse events related to β_2-receptor blockade. Intravenously, 1–5mg may be given for blood pressure control with the initial dose usually at the lower range. An effect is usually seen within 2–3 minutes and may last for up to 4 hours.[111] As with most β-adrenoceptor antagonists, metoprolol is particularly effective in patients with perioperative hypertension complicated by tachycardia. Metoprolol alone may not be effective, but by blocking the reflex tachycardia seen after administration of vasodilators, metoprolol may potentiate their effect. The PR interval and width of the QRS complex should be monitored for disorders of intracardiac conduction as with all β-blockers.

Atenolol has an elimination half-life of ≈6 hours. It is weakly protein bound and is excreted almost exclusively by the kidneys. The slower onset of action may make atenolol less appropriate for the perioperative treatment of hypertension. However, data in non-cardiac surgery have suggested a valuable effect in cardiovascular risk reduction[97] and more recent analysis suggests that its prolonged duration of effect may make it more suitable than metoprolol in managing perioperative cardiovascular risk.[102]

Propranolol is a non-selective β-blocker with strong membrane-stabilising properties and weak intrinsic sympathomimetic activity. It is highly lipophilic with effective transport across the blood brain barrier. It is extensively metabolised by the liver and has a half-life of 3–4 hours. Because of the nature of the perioperative period, propranolol is now rarely used for acute perioperative hypertension since other more modern drugs are preferred. In a recent study where the choice of perioperative β-blocker was left open to the physician, only 1% of patients received propranolol compared with 60% receiving metoprolol and 39% receiving atenolol.[118]

Labetalol has selective, competitive, α_1-adrenoceptor blocking and non-selective, competitive, β-adrenoceptor blocking activity. In humans, the ratio of α : β blockade has been estimated to be approximately 1 : 7 following intravenous administration, compared with a ratio of 1 : 3 following oral administration.[119] β_2-Adrenoceptor agonist activity has been demonstrated in animals, thus potentiating

a vasodilator effect. There is also experimental evidence of a membrane-stabilising effect. Intravenous labetalol has been shown to prolong atrio-ventricular nodal conduction time in common with other β-blockers and prolongs the atrial effective refractory period also. The effects on atrio-ventricular nodal refractoriness were inconsistent.

Labetalol may be given both by bolus administration and by continuous infusion. It has been shown to be more effective than esmolol for perioperative hypertension[120] and is effective either by bolus administration or by continuous infusion.[108] Its use has been described in a variety of settings.[109,110]

2.4.3 Agonists at Peripheral Receptors

Dopaminergic agonists are effective at dopaminergic receptors, and may cause splanchnic, cerebral and coronary vasodilatation when given intravenously. Dopamine, the parent compound, is also active at α- and β-adrenoceptors in a dose-dependent manner and is, therefore, unsuitable for blood pressure control. Dopexamine possesses β_2-adrenoceptor agonism in addition to dopamine D_{1A}-receptor agonism, and is also not suitable for blood pressure control.

Fenoldopam is a synthetic dopaminergic agonist without agonist adrenergic effects, although there is evidence of a mild α-adrenoceptor blocking effect and it may be particularly suited to controlling blood pressure in the perioperative period.[121-123] Initially studied in the setting of chronic heart failure, it became clear that fenoldopam was able to control blood pressure in a variety of settings including severe or malignant hypertension,[124-126] as well as perioperative hypertension. Both the renal and cardiac effects of fenoldopam compared favourably with other compounds, including nifedipine[123] and sodium nitroprusside.[122,125-127] Fenoldopam does not cross the blood-brain barrier and is a selective agonist at peripheral D_{1A}-receptors. Vascular effects include dilatation primarily of the renal, mesenteric and coronary vasculature.[128] There is also an increase in glomerular filtration rate and an increase in sodium and water excretion. Fenoldopam undergoes hepatic conjugation with no active metabolites and no adverse effects on cytochrome P450 isoenzymes.[129]

Fenoldopam is available in the US and some European countries, and it is to be hoped that a license for use throughout the EU will be available in due course. It is recommended for use for up to 48 hours for the acute or emergency control of blood pressure, and would appear to be one of a small number of vasodilators with a highly favourable profile for use in the perioperative period.[130] Studies of patients at risk from renal injury have so far not revealed consistent results.[131-133]

2.5 Drugs that Affect Calcium Channels

A number of calcium channels have been identified in humans, and of these the most important in the vasculature are the L-type channels, typified by a long-lasting effect. Blockade of calcium channels reduces the inward flow of calcium into the cell. In the myocardium, this may result in a reduction in calcium-facilitated calcium release from the sarcoplasmic reticulum and a down-shift in inotropic state. This may be relevant in patients requiring antihypertensive medication in the perioperative period, but it does not account for the primary mechanism of action. In vascular smooth muscle, calcium channel blockade and the resulting reduction in calcium influx into the smooth muscle cell will result in an inhibition of vasoconstriction and the resulting vasorelaxation causes the blood pressure to fall.[134]

There are three classes of calcium channel antagonists (i) the phenylalkylamines (verapamil); (ii) the dihydropyridine receptor antagonists (nifedipine, nimodipine, isradipine, amlodipine, nicardipine, clevidipine); and (iii) the benzothiapines (diltiazem). All three classes have drugs that are available as an injectable formulation. Verapamil is more appropriately used as an antiarrhythmic agent. Diltiazem has been recommended as an antiarrhythmic drug[85,135] and is also used effectively in the management of angina pectoris.

The dihydropyridine calcium channel antagonists are primarily systemic vasodilators and are particularly useful for the management of perioperative

hypertension. A number of compounds are available as injectable formulations, although their geographic availability varies markedly.

Dihydropyridines interact with the dihydropyridine receptor on the L- or T-type calcium channel, suggesting that an endogenous vasopressor might have an effect at this site.[136] The effect of blocking this receptor is to render the channel more likely to be in the closed state, with resultant reduction in calcium influx and vasodilatation.

The effects of dihydropyridine antagonists have been studied in a number of perioperative settings, including cardiac surgery.[137-143] Systemic and coronary vascular resistance are reduced, blood pressure falls, cardiac filling pressures are maintained, and cardiac and stroke output are increased. The lack of venodilatation and thus maintenance of preload is responsible for increasing stroke output and preserving pulmonary artery and pulmonary capillary wedge pressure. However, in patients with primary pulmonary hypertension, there is evidence to suggest a therapeutically useful pulmonary vasodilator effect.[144,145]

Experimental studies have suggested that dihydropyridines have a mild negative inotropic effect. In humans, this is usually modified by sympathetic activation so that the overall effect seen is neutral or a mild increase in inotropy. However, detailed analysis has revealed a negative inotropic effect.[146]

Isradipine, nicardipine and nifedipine are used as systemic vasodilators. Clearly, the intravenous route of administration is preferable. Intranasal nifedipine has been described as safe and effective, although it should be noted that the patients under study were mostly those with treated hypertension with poor control of DBP preoperatively.[147] In contrast, Varon and Marik[148] have condemned the use of sublingual nifedipine for hypertensive emergencies and 'pseudo-emergencies', and others have called for a moratorium on its use for safety reasons.[149] Many of the adverse reports refer to the use of sublingual nifedipine in unmonitored patients presenting as hypertensive emergencies or urgencies.[148] Despite numerous anecdotal reports of the safe use of intranasal nifedipine in the perioperative setting, it is the author's practice to avoid sublingual or intranasal nifedipine for perioperative blood pressure control.

Other compounds have also been described. Nimodipine appears to have effects largely confined to the cerebral circulation and has been reserved for cerebral vasospasm.[150] Clevidipine is a new compound with an ultrashort duration of action due to its metabolism by tissue esterases in a similar manner to esmolol. Clevidipine has a half-life of ≈1 minute in cardiac surgery patients[151] and a context-sensitive half-time is <2 minutes for up to 12 hours of administration.[152] Infusions of clevidipine have been shown to produce pharmacodynamic effects similar to the other dihydropyridines described earlier.[137,140]

2.6 Others

There are a number of other classes of drugs that have vasodilator effects, although they have not become established for perioperative blood pressure control.

Phosphodiesterase (PDE) inhibitors have shown a direct vasorelaxant effect, as well as an inotropic effect. In the vasculature, the increase in 3′5′ cAMP leads to phosphorylation of light chain kinase. This results in a reduction of its affinity for the calcium-calmodulin complex and dephosphorylation of myosin light chains and leads to vasodilatation. PDE also hydrolyses cyclic guanosine monophosphate, which may also contribute to the vasodilator effect.[153] However, PDE type 3 inhibitors have not been widely used for blood pressure control, partly because they are more commonly used as inotropic agents. Nonetheless, many studies have reported a fall in systemic vascular resistance and a small but insignificant fall in blood pressure following intravenous milrinone. In one study, in patients following cardiac surgery, milrinone caused a reduction in elevated blood pressure but not a further reduction in normal or low blood pressure.[154] This may make the drug suitable for use in the setting of perioperative hypertension associated with a low output state, for example, and in the perioperative patient with hyperten-

sive heart failures provided suitable attention is paid to fluid balance.

ACE inhibitors will reduce the generation of angiotensin-II and thus reduce the effects of vasoconstriction, aldosterone secretion and sympathetic activation. All of these actions contribute to the development of hypertension. Angiotensin-II-receptor antagonists act by binding to specific membrane-bound receptors that displace angiotensin-II from the angiotensin type 1- receptor subtype (AT_1). Therefore, these drugs function as selective blockers. Angiotensin-II pressor effects are mediated by AT_1-receptors, found predominately in vascular and myocardial tissue, the liver, the zona glomerulosa in the adrenal cortex and in some areas of the brain.

Both of these groups of drugs have been shown to be highly effective in the management of chronic hypertension and chronic heart failure, and many high-risk surgical patients may be taking either ACE inhibitors or angiotensin-receptor antagonists preoperatively. Should patients receiving either type of drug discontinue their medication before routine surgery, and if so will they be more likely to need further treatment to control blood pressure in the perioperative period?

Early studies suggested that continuation of ACE inhibitors and inhibitors up to the day of surgery was associated with an unacceptable degree of hypotension on induction of anaesthesia. Although this may be successfully managed with crystalloid transfusion, occasionally vasopressor treatment is necessary, and this in turn may be more complex as a result of variable responsiveness to α-adrenoceptor agonists.[155] Thus, the initial recommendation was to discontinue treatment at least 24 hours preoperatively,[156,157] more recently modified to 10 hours. In addition, hypotension and difficulty in weaning from cardiopulmonary bypass was also noted, presumably as a result of the accumulation of bradykinin, a compound normally metabolised by ACE, resulting from the inflammatory cascade induced by cardiopulmonary bypass.[158] Other work has challenged these recommendations,[159] although some centres still recommend withdrawing ACE inhibitors in the days before cardiac surgery.[160]

ACE inhibitors are without doubt amongst the most valuable cardiovascular drugs in current practice. Although not the subject of this article, their value in hypertension, heart failure and acute myocardial infarction is generally undoubted. However, despite the availability of an injectable preparation, the use of intravenous ACE inhibitors has not become widespread for perioperative hypertension. While reduction in systemic vascular resistance is a well observed phenomenon, blood pressure is usually well maintained and the efficacy of treatment as a means of controlling blood pressure is therefore unpredictable.[161,162]

2.7 Nitric Oxide Donors

Nitric oxide (NO) is a profoundly important substance in the control of vascular tone. An endogenous compound, it is normally secreted by the vascular endothelium in response to a number of stimuli that may activate receptors coupled to phospholipase C, which leads to an increase in inositol triphosphate in the cytosol. This results in an increase in calcium release from the sarcoplasmic reticulum which, once linked to the binding protein calmodulin, activates NO synthetase and leads to the conversion of L-arginine to citrulline with the liberation of NO.

A number of drugs act as a source of NO promoting vasorelaxation. NO gas is given by inhalation, but it is rapidly scavenged by haemoglobin and is quickly deactivated, with a half-life of <1 minute. As a result, it causes selective pulmonary vasodilatation and is unsuitable for systemic blood pressure control.

Other intravenous drugs are suitable and are discussed in sections 2.7.1–2.7.2. These drugs are well established in clinical practice and so are covered in outline only.

2.7.1 Nitrites

Sodium nitroprusside is arguably the most effective vasodilator in both arterial and venous vasculature in clinical use, and is almost invariably effective provided steps are taken to control a reflex increase in heart rate. Simultaneous administration of a β-blocker is therefore commonplace. The efficacy of

sodium nitroprusside is suggested by the fact that it is the drug most commonly used as comparator for newer agents.

Sodium nitroprusside is a highly unstable molecule. It is light sensitive and susceptible to sunlight; hence, the formulation must be provided and administered using light-protected equipment. The molecule is broken down in erythrocytes with the consequent liberation of cyanide ions and NO, which acts on the vascular endothelium to produce vasorelaxation. The cyanide ions are converted in the liver by rhodonase to thiocyanate, a reaction dependent on a sulfur donor such as thiosulfate. Thiocyanate undergoes renal excretion, and the presence of thiosulfate or another sulfur donor is an important factor in preventing the build up of cyanide ions and cyanide toxicity.[163,164]

Sodium nitroprusside has a rapid onset and ultrashort duration of action. Its half-life is of the order of 2–4 minutes, although the metabolite thiocyanate has a half-life of several days. It is recommended that the duration of treatment should not exceed 72 hours, whereupon plasma thiocyanate concentrations should be monitored. In practice, the combination of sodium nitroprusside with other agents has meant that the problem of cyanide toxicity is not a problem in the perioperative patient.

Sodium nitroprusside causes a rapid reduction in tone in most vascular beds, including muscle, skin and the splanchnic circulation.[122,137-139] Systemic pulmonary and coronary vascular resistance have all been shown to fall. In circumstances where resting vascular tone is high, a reduction may induce a significant increase in flow. Thus an increase in cerebral blood flow and hence in intracranial pressure may result.[165] Sodium nitroprusside reduces overall coronary vascular resistance, and may therefore induce intracoronary steal; it is not an effective anti-ischaemic agent in angina.[166]

2.7.2 Nitrates

In common with other nitrates, nitroglycerin must be de-nitrated in order to produce NO, the active component. A number of denitration mechanisms have been proposed, including reaction with sulfydryl groups, or dependent on the actions of glutathione S transferase, cytochrome P450 and xanthine oxidoreductase. More recent evidence suggests that the conversion of nitroglycerin to 1,2 glyceryl dinitrate and NO is catalysed by mitochondrial aldehyde dehydrogenase.[167]

The primary use of nitroglycerin and other nitrates, including isosorbide mononitrate, is as antianginal agents. They are effective since they have a beneficial effect on coronary blood flow, via selective vasodilation of epicardial coronary arteries, and by venorelaxation and consequent reduction in left ventricular end-diastolic pressure and hence subendocardial compression. Myocardial demand is also reduced consequent on a reduction of left ventricular wall stress.[167]

Nitrates, and in particular nitroglycerin, are commonly used for perioperative blood pressure control, particularly in the setting of cardiovascular surgery.[19,141] Stepwise increases in an intravenous infusion of nitroglycerin cause a reduction in venous tone and central venous pressure, with a gradual reduction in systemic pressure. Bolus doses, on the other hand, cause an immediate and significant reduction in arterial pressure. The greater effect on the venous side of the circulation may be a reflection of different background rates of NO production in the vascular endothelium of veins and arterioles. Comparative studies of nitroglycerin with other vasodilators have shown nitrates to be similarly effective, but in clinical practice, concomitant administration of either a β-blocker, or a drug with more direct effects on arteriolar tone, is necessary.

Hydralazine was previously used as oral treatment, for example in hypertension associated with pregnancy, but this is now less common. The untoward effects seen with long-term therapy, including a lupus like syndrome in <10% of patients, are not a feature of short-term intravenous use. The mechanism of action when given intravenously is not clear. Hyperpolarisation of muscle cells probably through the opening of potassium channels, inhibition of the release of calcium from the sarcoplasmic reticulum in smooth muscle, reduction in calcium stores in the sarcoplasmic reticulum, and stimulation of the formation of NO by the vascular endothelium have all

been implicated. Hydralazine has a relatively slow onset to peak effect and care must be taken with initial administration. It is effective in combination with other drugs, including nitroglycerin and β-blockers. Although primarily used in systemic hypertension, some have advocated its use in pulmonary hypertension also.

3. Future Issues: The Impact of Genomics

Previous studies have noted the relative genetic contribution to differences in both SBP and DBP levels between individuals. In one study of non-Hispanic Whites, the proportion of variation of SBP attributable to genetic differences was estimated to be 0.37,[168] with similar values reported for DBP level.[169]

Although single genes have been identified that may be responsible for several rare mendelian forms of hypertension,[170] their low frequency in the general population diminishes their public health impact overall. More typically, blood pressure levels are controlled by a complex interaction of processes that influence cardiac output and systemic vascular resistance.[171,172] Since many physiological, biochemical and anatomical systems may be contributory, multiple genes may potentially be involved in influencing blood pressure in most individuals. These genetic influences may affect either vasopressor or vasorelaxant mechanisms, and the complexity of blood pressure regulation suggests that there is substantial genetic heterogeneity. Thus, the relationship between blood pressure and the genotype at relevant loci may not be common to different individuals.

Recent studies have demonstrated genetic linkages that potentially influence the blood pressure level, for example at the angiotensinogen gene locus,[173,174] with identification of variants that may contribute to essential hypertension; although this finding remains controversial.[173,175,176]

Currently, genome-wide linkage analyses are being undertaken to identify loci involved in the development of hypertension.[177]

In addition to determining relationships between gene loci and the development of hypertension, there is also a relationship between the genome and the inter-individual variability in the efficacy of antihypertensive therapy. Traditionally, pharmacokinetic mechanisms that determine the blood and effector site concentrations, as well as absorption, distribution, excretion and metabolism have been found to be most influential. However, genetic variations may alter any of the proteins involved in any of these mechanisms and thus contribute to variations in drug response. Also, since genes may influence the controllers of the physiological determinants of blood pressure, they may affect the effectiveness of antihypertensive therapy.[178]

Although single-gene polymorphisms with large effects on drug metabolism have been identified, it is unlikely that these will be widely relevant to current antihypertensive drug therapy. Agents such as hydralazine, known to be metabolised predominantly by known polymorphic enzymes with large inter-individual differences in activity, are now rarely used. For most current antihypertensive drugs, pharmacodynamic mechanisms are more important in determining variation in blood pressure responses. The dose-response relationships for most modern antihypertensive drugs are flat and the magnitude of the blood pressure lowering effect is similar for drugs within a class, despite considerable differences in their pharmacokinetic properties. As a result, interest is turning to identifying genes that influence the pharmacodynamic determinants of blood pressure response.[178,179]

A number of interesting findings have been discovered. For example, the Gly460Trp polymorphism in humans with essential hypertension has been shown to affect the blood pressure response to diuretic treatment with furosemide or hydrochlorothiazide,[180,181] thus demonstrating how a gene that contributes to hypertension via a particular physiological mechanism, in this case by increased renal sodium reabsorption and volume expansion, can serve as a candidate gene to influence blood pressure response to an antihypertensive agent that targets this mechanism. A genome scanning ap-

proach may be more effective in yielding further information in the future.

As the genetic nature of each individual's susceptibility to hypertension is elucidated, so we may become clearer about which drugs alone or in combination may constitute effective therapy.

A third area of future study concerns our understanding of which patients are susceptible to organ damage as a result of hypertension. We could describe this as the genetic basis of risk assessment in the hypertensive patient. There has already been much work in this area and the impact of genes may be felt in a number of ways. First, genes may cause disease of a target organ independent of any effect on blood pressure. However, elevated blood pressure may simply aggravate or accelerate the effect of such genes on the primary disease process. Secondly, genes may directly influence blood pressure and elevated blood pressure may in turn directly contribute to the development of target-organ disease. Thirdly, genes may contribute to target-organ damage both through effects on blood pressure and via independent pathways separate from blood pressure.

Previously, our understanding has been that target-organ damage is linked to the level of chronic hypertension which, if adequately controlled, will restrict the development of target organ damage. However, recent data suggest that this relationship may not be so simple. Twin and family studies have estimated the heritability of the left ventricular mass as between 22% and 59%.[182,183] Genetic variation probably contributes to inter-individual differences in the left ventricular mass by virtue of effects on blood pressure as well as via pathways that are not captured by measurements of blood pressure.

Recently, a number of important studies have identified genetic susceptibility to adverse effects seen in high-risk surgery, including myocardial infarction,[184] sepsis,[185] stroke,[186] pro-inflammatory upregulation,[187] bleeding[188] and renal injury.[189] Given the nature of these adverse events, it is possible that many of the genetic variants involved may be associated with the development of hypertension also, and that in due course therapies may be developed to target both the adverse event and also the effect on blood pressure.

4. Conclusions

Since there is no drug currently available that can be described as ideal, and given the heterogeneity of patients in whom perioperative blood pressure control is required, it is likely that a range of agents will continue to be needed, suited to different patients and in different settings. Thus, future pharmacological research is necessary but what direction will such research take?

Pharmacokinetic developments will continue to be important. The development of esmolol and clevidipine has clearly shown the value of drugs with a mechanism of inaction or metabolism that is ultra-fast. Where receptor interaction is variable, greater receptor specificity may be invaluable; the β_1 specificity of the ultra short-acting β-blocker landiolol[190] and the dopaminergic receptor specificity of fenoldopam are examples of developments in this direction. Alternatively, a combination of effects, for example combined α- and β-blockade, β-blockade and calcium channel blockade, or PDE inhibition and β-blockade, are all attractive possibilities.

Novel mechanisms of action may be revealed as a consequence of our understanding of the genetic aetiology of hypertension, as described in section 3.

New drugs take years and cost millions of dollars to bring to the market. Thus, the agents of the near future are probably already under study.

The importance of cardiovascular drugs as a means of maximising cardioprotection in the perioperative period cannot be overemphasised. This has been a vital area of research over the last decade, and will continue to be so, fuelled inevitably by an increasingly sick and aged population undergoing elective surgery. Current evidence suggests that of the antihypertensive drugs, β-blockers, ACE inhibitors and α_2-adrenoceptor agonists may have a significant role to play, although there is doubt about the long-term benefits of angiotensin-II receptor blockade.[191,192] Future studies with all these drugs should now concentrate on maximising benefit and

minimising adverse events in at-risk populations. Equally, it will be important to establish whether it is the sympatholytic nature of these drugs that accounts for their efficacy or whether, more specifically, blood pressure control is important. Current evidence would suggest that the former is more important in all but the most specialised surgical settings.

Finally, the impact of genomic research on future pharmacological research and development will be immense. The mapping of the human genome and subsequent research has improved our understanding of the genetic causes of hypertension, the genetic susceptibility to target-organ complications and the pharmacogenetics of antihypertensive therapy.

Acknowledgements

No financial support was received by the author with respect to this manuscript, and there are no conflicts of interest.

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Correspondence: Dr *Robert Feneck*, Department of Anaesthesia, Guys and St Thomas' Hospitals, London, SE1 7EH, England.
E-mail: rob_feneck@msn.com