CARDIOVASCULAR PHARMACOLOGY FOR ANAESTHETISTS

Dr Ute Schröeter, formerly of Spitalzentrum, Biel, Switzerland and Dr James Rogers, Frenchay Hospital, Bristol, UK.

INTRODUCTION

The subject of cardiovascular pharmacology is diverse, and this article concentrates on areas relevant to the anaesthetist. The pathophysiology of common diseases of the heart and circulation is discussed before considering the drugs used for treatment.

In general, the action of drugs is either by (a) alteration of myocardial contractility or heart rate, (b) alteration of conduction of the cardiac action potential or, (c) vasodilatation or vasoconstriction of coronary and peripheral vessels. This article aims to build on subjects covered in previous issues, in particular: "The Autonomic Nervous System" 1995;5: 3-6, "Cardiovascular Physiology" 1999; 10: 2-8, and "Pharmacology of Vasopressors and Inotropes" 1999; 10: 14-17.

ANGINA

Pathophysiology

The normal myocardium accounts for 11 % of the total body oxygen consumption, but the coronary circulation receives only 4 % of the cardiac output. In other words, considering its metabolic demands, the myocardium is one of the more poorly perfused tissues in the body. As a consequence, any pathological disturbance that changes the *myocardial oxygen balance* can result in myocardial ischaemia. This balance of myocardial oxygen supply against demand is dependent on the following:

Myocardial oxygen supply	Myocardial oxygen demand
Heart rate	Heart rate
Coronary perfusion pressure	Ventricular preload and afterload
Arterial oxygen content	Contractility
Coronary artery diameter	

The most common cause of angina is the build up of *atheroma*, composed of cholesterol and other lipids, in larger coronary arteries. The obstruction to blood flow may become so severe that not enough blood can pass through the arteries to supply the myocardium when oxygen demand increases, for example during exercise. The ischaemic muscle produces the characteristic symptoms of *angina pectoris*, probably because metabolites produced by myocardial contraction accumulate in the poorly perfused tissue. These symptoms include retrosternal chest pain or tightness, which often radiates to the arms. The pain is usually caused or increased by exercise, and relieved by rest and treatment with nitrates.

Anti-anginal drugs

Treatment of patients with significant coronary artery disease aims to achieve an "even" myocardial oxygen balance. Drugs are used to; (a) reduce preload (nitrates), (b) reduce heart rate, myocardial work and oxygen consumption (beta-blockers), (c) maximise coronary vasodilatation (calcium channel blockers).

Nitrates are the drugs of first choice. Their main action is peripheral vasodilation, either venous (low doses), or both venous and arterial (higher doses). This vasodilation is mediated by production of nitric oxide (NO), and increased levels of intracellular guanosine 3',5'-monophosphate (cGMP) in vascular smooth muscle. The resulting pooling of blood in the capacitance vessels (veins) reduces venous return and decreases ventricular volume. This reduction in distension of the heart wall decreases oxygen demand and

the pain of angina is relieved quickly. At the same time nitrates improve myocardial oxygen supply by increasing the coronary blood flow to the endocardium. Cardiac output is usually unchanged or decreased slightly, and a reflex tachycardia occurs in normal subjects. However in patients with heart failure, who have a high systemic vascular resistance, cardiac output may increase and there is little change in the heart rate.

Glyceryl trinitrate (GTN) is a short-acting nitrate, with a duration of action of 30 minutes. It is more useful in preventing attacks of angina than in stopping them once they have begun. It may be given by a sublingual, transdermal or intravenous route. In the latter case, between 40-80% of the dose may be absorbed by the plastic giving set. Longer acting nitrates are more stable and may be effective for several hours, depending on the drug and formulation used. (eg. isosorbide dinitrate, isosorbide mononitrate).

Unwanted effects of nitrates include dilation of cranial vessels causing headaches, which can limit the dose used. More serious side effects are tachycardia and hypotension. These result respectively in increased myocardial oxygen demand and decreased coronary perfusion, both of which have an adverse effect on myocardial oxygen balance. Another well recognised problem is the development of tolerance to nitrates. Blood vessels become hypo- or non-reactive to the drugs, particularly when large doses, frequent dosing regimes and long acting formulations are used. To avoid this, nitrates are best used intermittently, allowing a few hours without treatment in each 24 hours period.

Beta blockers These are used to prevent angina as well as to treat hypertension, by blocking beta 1 receptors in the heart. In addition to this blocking action, some beta-blockers can actually stimulate the receptors at a low level. This so called intrinsic activity can be a disadvantage when treating angina. Drugs such as atenolol and metoprolol are the drugs of choice, because they are cardioselective, i.e. only work on beta-1 receptors, and not the beta-2 receptors elsewhere in the body.

Most side effects of beta blockers are the consequence of their blocking action. *Bronchoconstriction* (mediated by beta-2 receptors) is normally of little importance. However in asthmatics it can be life-threatening, and beta blockers should not be used in these patients. *Cold extremities, worsening of peripheral vascular disease, hypoglycaemia* and impotence are also caused by blockade of beta-2 receptors. Some patients with heart disease need a sympathetic "drive" to the heart to maintain adequate cardiac output, and blockade of beta-1 receptors in these patients can cause heart failure.

Calcium antagonists These drugs act by blocking the calcium channels which open in response to depolarisation of the cell membrane (voltage sensitive channels). Such channels occur in many different cells of the body, but the important pharmacological effects of these drugs are restricted to cardiac and smooth muscle. Calcium antagonists are divided into three sub-groups based on their chemical structure;

(a) papaverine derivatives e.g. *verapamil*

(b) benzothiazepines e.g. *diltiazem*

(c) dihydropyridines e.g. *nifedipine, amlodipine*

Calcium antagonists reduce afterload (by arterial vasodilation), dilate coronary arteries, and reduce cardiac work, thus improving myocardial oxygen balance. Verapamil and diltiazem also have an anti-arrhythmic effect, whereas the dihydropyridines predominantly affect vascular smooth muscle. Adverse effects of calcium antagonists include postural hypotension, flushing, peripheral oedema and constipation. All calcium antagonists have a negative inotropic effect, especially verapamil, and should not be used in patients in cardiac failure.

CARDIAC FAILURE

Introduction

Cardiac failure is common and the incidence is increasing in many countries. Despite adequate ventricular filling, the failing heart is unable to deliver as much blood as the tissues require, even when myocardial contractility is increased by the sympathetic nervous system. The causes of heart failure are numerous, but can be classified as follows: (a) endocardial disease, (b) myocardial disease, (c) pericardial disease and, (d) congenital heart disease. Cardiac failure may be precipitated by the factors listed below:

Disturbance of heart rate or rhythm

- Drugs
- Anaemia
- Infection or fever
- Pulmonary embolism
- Fluid overload
- Hypertension
- Pregnancy
- Hyper- or hypothyroidism

Pathophysiology

Cardiac output is the product of heart rate and stroke volume (CO = HR x SV). Stroke volume is determined by three factors; *preload, afterload and contractility*. The effect of changes in any of these variables can be illustrated graphically by the "Starling curve". In cardiac failure the Starling curve is displaced downwards, meaning that increases in end-diastolic ventricular filling volumes (preload) are required to maintain performance.

There are adaptive mechanisms to improve cardiac output, including sodium and water retention by activation of the renin-angiotensin-aldosterone system. This increases blood volume, and thereby preload, but may in turn cause unwanted oedema in both peripheral tissues and the lung. A rise in catecholamine release leads to increased heart rate and contractility, but also an increase in systemic vascular resistance (afterload). In long standing cardiac failure there is hypertrophy of the muscle mass and enlargement of the ventricles.

Drugs used in heart failure

Where possible, underlying disease and the precipitating factors mentioned above should be investigated and treated. The treatment of heart failure aims to:

(a) optimise ventricular filling pressures	*Diuretics* *Nitrates*
(b) improve contractility (inotropic drugs)	*Digoxin* *Sympathomimetic agents* *Phosphodiesterase inhibitors*
(c) reduce cardiac work by reducing afterload (vasodilators)	*ACE inhibitors* *Prazosin*

Diuretics increase the excretion of sodium and water. By reducing the circulating volume they reduce preload and oedema. Loop diuretics such as frusemide are often used in acute as well as chronic heart failure. Low serum levels of potassium, calcium and magnesium are a common side-effect. At high parenteral doses frusemide may cause renal failure (interstitial nephritis) and deafness (auditory nerve damage), especially when it is given rapidly. Toxic effects are more common when frusemide is given in combination with aminoglycoside antibiotics or to patients with impaired renal function.

Nitrates These are used in the overdistended, acutely failing heart to reduce preload, pulmonary venous pressure and oedema. Their mode of action is discussed above.

Inotropic drugs

Digoxin is used to treat heart failure, especially when associated with atrial fibrillation. It is discussed in detail below. Sympathomimetic agents such as dopamine and dobutamine are given by intravenous infusion in severe, acute heart failure. Phosphodiesterase inhibitors such as milrinone improve contractility by increasing myocardial intracellular calcium. They are given in severe heart failure unresponsive to other drugs.

Angiotensin converting enzyme (ACE) inhibitors Drugs such as **captopril** are potent arterial and venous vasodilators. They block the renin-angiotensin system and reduce both preload and afterload, with a resulting increase in cardiac output. Despite the fall in arterial pressure the sympathetic system is not activated, and the decrease in heart rate improves the myocardial oxygen balance. Increased renal blood flow and reduced release of aldosterone causes an increased excretion of sodium and water, thus reducing circulating volume. ACE inhibitors are the most appropriate vasodilators for the long term treatment of heart failure.

Prazosin dilates coronary arteries, peripheral arterioles and veins by blocking alpha-1 receptors. Afterload is reduced, cardiac output increases and there is little reflex tachycardia.

ARRHYTHMIAS

Pathophysiology

Cardiac arrhythmias are common in the peri-operative period (see also page 16) but most are benign and cause no harm to the patient. Arrhythmogenic factors include drugs, ischaemia and altered biochemical and physiological states. Disturbances of cardiac rhythm, although complex, can be classified on the basis of electrophysiology as follows:

(a) **Arrhythmias of sinus origin:** electrical conduction follows the normal pathway but can be either too fast, too slow or irregular.

(b) **Ectopic rhythms:** these can be due to either abnormal automaticity (spontaneous discharge) or re-entry. In the former, single or multiple groups of myocardial cells take over as the pacemaker, giving either atrial or ventricular ectopic rhythms. Re-entry tachycardias involve the cardiac impulse being transmitted to a functional "ring" of conducting tissue, one side of which has a unidirectional (one-way) block. In this situation the impulse is conducted in a circular fashion in the ring, re-exciting the neighbouring myocardium immediately after its refractory (unresponsive) period. Re-entry mechanisms are implicated in atrial flutter and both supraventricular and ventricular tachycardias.

(c) **Conduction blocks:** these can occur at the level of either the atrioventricular node (first, second and third degree blocks) or the His-Purkinje fibres (bundle branch blocks).

(d) **Pre-excitation syndromes:** in this situation the normal delay at the atrioventricular node is bypassed by an accessory pathway, leading to premature ventricular depolarisation. Wolf-Parkinson-White and Lown-Ganong-Levine are the two most common pre-excitation syndromes.

Anti-arrhythmic drugs

The Vaughan-Williams classification of anti-arrhythmic drugs is on the basis of mechanism of action. Although widely used, it does not include digoxin and adenosine, which both have useful anti-arrhythmic actions.

Class I

Membrane stabilising drugs: fast depolarisation of the cell membrane is inhibited by blocking the inward flux of sodium ions. This class is further sub-divided into three groups based on the effect on duration of the action potential. Lignocaine is the most widely used drug in this class, and can be used for all forms of ventricular arrhythmia. Other membrane stabilising drugs include quinidine, procainamide, mexiletine and flecainide.

Class II

Beta-blockers: these drugs reduce automaticity, and increase the action potential duration in the ventricles as well as the refractory period at the atrioventricular node. Examples include propranolol, metoprolol and the shorter acting esmolol.

Class III

Prolongation of action potential and refractory period: amiodarone is the drug of choice, although bretylium is also used. They have an anti-fibrillatory effect by increasing electrical stability.

Class IV

Calcium antagonists: verapamil is the only useful agent, and slows conduction at the atrioventricular node in the treatment of supraventricular arrhythmias.

Digoxin is a cardiac glycoside, and sometimes classified as a Class V drug. It is the only anti-arrhythmic drug available for the treatment of atrial fibrillation that does not have negative inotropic or vasodilator effects. It is therefore used widely for heart failure as well as arrhythmias. Its direct action is to block the sodium/potassium ion exchange pump in the cell membrane. This eventually causes a rise in calcium ions within the cell, which increases contractility. Digoxin slows the conduction of the action potential, mostly at the atrioventricular node, but also in other parts of the heart. Digoxin also acts indirectly by increasing parasympathetic activity via the vagus nerve, further slowing atrioventricular node conduction. The drug is used to control the heart rate in atrial fibrillation, by limiting the ventricular response to atrial discharge.

High doses of digoxin can cause serious arrhythmias, such as complete heart block and ventricular ectopic beats,

which may lead to ventricular tachycardia or fibrillation. Less serious side-effects are nausea, vomiting, visual disturbance and headache, but these may precede toxicity. Plasma levels can be measured to ensure therapeutic levels are not exceeded. Some factors enhance toxicity, such as hypokalaemia, hypomagnesaemia, hypercalcaemia, hypoxia, acidosis and myocardial ischaemia. The dose of digoxin must be reduced in renal failure, and if there is a known drug interaction (e.g. amiodarone, verapamil, quinidine).

Adenosine is a naturally occurring molecule which is a metabolite of adenosine monophosphate. It acts via specific adenosine receptors to cause coronary vasodilation and reduced conduction at the sino-atrial and atrioventricular nodes. It is particularly useful in treating re-entry supraventricular tachycardias, but has no effect on ventricular tachycardia. It has a very short half-life (10 seconds), and is given by rapid intravenous injection. The short duration of action and low incidence of adverse effects makes adenosine useful in diagnosing broad complex tachycardias as either supraventricular or ventricular in origin.

HYPERTENSION

Pathophysiology

In most patients with raised blood pressure there is no obvious cause; this is called *essential hypertension*. The pathogenesis of hypertension is complex but the following factors have been implicated: (a) increased sympathetic activity, (b) sodium retention and an increased circulating volume, (c) increased vascular rigidity and reactivity, (d) increased circulating catecholamines and activation of the renin-angiotensin-aldosterone system, and (e) abnormal baroreceptor responses. High blood pressure is associated with a reduced life expectancy, because of an increased risk of stroke and coronary artery disease; also other end-organ disease, such as retinopathy and renal failure.

Anti-hypertensive drugs

Arterial pressure increases with age and therefore there is no absolute value at which treatment should be started. Untreated hypertension leads to increased perioperative morbidity and mortality. In the presence of other cardiovascular risk factors such as diabetes, hyperlipidaemia or smoking, the threshold for treatment should be lower. As a general rule elective surgery should be delayed if the resting diastolic pressure is greater than 110 mm Hg.

Based on the pathogenesis of essential hypertension described above, there are different classes of anti-hypertensive drugs. They are used alone or in various combinations. *Diuretics* (either thiazide or loop diuretics) reduce sodium and extracellular volume and are often the first-line drugs. Another important group are the vasodilators, such as *ACE-inhibitors, calcium antagonists,* and the direct vasodilator *hydralazine*. Adrenergic blocking agents such as *beta-blockers* and the alpha 1-receptor antagonist *prazosin* are also widely used.

Treatment of severe hypertension

Although severe hypertension (e.g. diastolic pressure above 140 mmHg) can often be managed with oral treatment, this may not be suitable for the peri-operative patient, or when there are life threatening complications such as encephalopathy or heart failure. In these situations blood pressure can be controlled with the intravenous agents described below, which have the advantage of a rapid onset of action. The dose should be titrated against the response, because rapid falls in blood pressure can cause reduced cerebral perfusion and infarction. Before starting such treatments in the peri-operative patient, factors which may be aggravating the hypertension should be identified and treated. These include inadequate analgesia, hypothermia, hypoxia and withdrawal of normal anti-hypertensive drugs.

Labetalol This drug is both an alpha-1 and beta adrenergic receptor blocker, with a ratio of alpha:beta activity of about 1:5. As well as emergency treatment of severe hypertension, it is also used in the treatment of pre-eclampsia and to provide hypotension for certain surgical procedures. Labetalol has a half-life of between three and six hours depending on the dose given, and can cause hepatic damage, even after short periods of treatment. It is given intravenously in increments of 5-10mg up to a maximum of 200mg.

Hydralazine is an arteriolar vasodilator and thus reduces systemic vascular resistance, causing a reflex tachycardia. It is widely used in hypertension associated with pre-eclampsia, but its onset of action may be up to 20 minutes. Headache, nausea, vomiting, and flushing are common side effects, and it can cause angina in patients with ischaemic heart disease. In the obstetric patient the aim is to keep the blood pressure below 170/110 mmHg, using doses of 5-10mg which can be repeated after 30 minutes if necessary.

Sodium Nitroprusside (SNP) This acts directly on vascular smooth muscle and causes arteriolar and venous dilation. As a consequence blood pressure falls and a reflex tachycardia occurs. SNP acts very rapidly and the duration of action is only a few minutes. The drug can produce toxicity by production of cyanide, and there are maximum recommended doses for both acute and longer term use. GTN, which is discussed elsewhere, can also be used for rapid control of high blood pressure.

CARDIOVASCULAR EFFECTS OF ANAESTHETICS

Inhalational agents

All volatile agents depress myocardial contractility, but this effect is most marked with *halothane* and *enflurane*. With the exception of halothane they all decrease systemic vascular resistance, contributing further to the fall in blood pressure and resulting in a reflex tachycardia. During halothane anaesthesia systemic vascular resistance is unchanged and, due to vagal stimulation, bradycardias and nodal rhythms are common. Unlike other volatile agents halothane sensitises the heart to the arrhythmogenic effects of catecholamines, and ventricular ectopics are often seen. High levels of circulating catecholamines can cause ventricular tachycardia or ventricular fibrillation, especially in the presence of hypercarbia, which can occur in a patient spontaneously breathing halothane. *Ether* causes sympathetic stimulation, catecholamine release and, to a certain degree, vagus nerve blockade. As a result there is an increase in cardiac output, heart rate and systemic vascular resistance, so blood pressure is well maintained.

Intravenous induction agents

Most induction agents are cardiovascular depressants. The greatest effect is seen with *propofol*, which may cause a marked fall in blood pressure, systemic vascular resistance and heart rate, the latter due to central vagal stimulation. *Thiopentone* has similar effects, although less pronounced, and there is a reflex tachycardia mediated by the baroreceptor reflex. This can result in increased myocardial oxygen consumption and a consequent increase in coronary blood flow. Benzodiazepines such as *midazolam* and *diazepam* are associated with cardiovascular stability, and only high doses will cause cardiovascular depression. *Etomidate* provides the most cardiovascular stability, with only slight changes in haemodynamic variables. Etomidate has little effect on myocardial oxygen balance. *Ketamine*, in contrast to other induction agents, is a potent cardiovascular stimulant by increasing sympathetic nervous discharge, although its *direct* effect on the myocardium is negatively inotropic. On induction there is a marked rise in heart rate and blood pressure caused by central nervous stimulation and an increase in circulating catecholamines.