This article provides an overview of cardiovascular pharmacology by relating the mechanism of action of different classes of drugs to their effect on the control of the cardiovascular system. It will cover both newer types of drug, and recent advances in the understanding of older drugs. Understanding the mechanism of action of any new drug allows anaesthetists to incorporate new drugs into their clinical practice.

The cardiovascular system uses a complex series of control mechanisms to maintain homeostasis. These controls utilise multi-layered, inter-related mechanisms which help to minimise system redundancy and duplication. They utilise diverse methods from simple molecular function to principles of fluid dynamics in whole organs. This complexity has led to a diverse array of therapeutic agents being developed which target different areas. This diversity causes difficulty in constructing a system for classifying drugs which can also explain their mode of action.

However, the cardiovascular system can be visualised as a simple three-component model: (i) a reservoir for fluid; (ii) a pump; and (iii) a variable resistance circuit to distribute the fluid. These are, in turn, the ‘preload’, ‘cardiac contractility’, and the ‘afterload’. When ‘heart rate’ is added, this classification allows placement of structurally unrelated drugs into clinically useful groupings.

**Preload** is defined as the cardiac myofibril length (or chamber volume) in end diastole. It is influenced by ‘inflow’ characteristics (blood volume and venous capacitance) and ‘outflow’ characteristics which are determined by ventricular contractility and compliance.

**Contractility** is defined as the inherent inotropic ability of the heart, independent of all other determinants of cardiac output. It is influenced by intracellular calcium availability, ventricular wall tension, myocardial oxygen delivery and demand. It may be impaired by deformation of the chamber wall, poor perfusion from acute ischaemia, reperfusion injury or infarction. Contractility can be impaired by dysrhythmias, slow and fast, and by ectopic electrical activity causing dysfunctional contraction.

**Heart rate** is a major determinant of cardiac output (cardiac output = stroke volume x heart rate) and drugs altering heart rate may have significant systemic effects. For example, tachycardia will influence output by reducing time for diastolic chamber filling and by reducing diastolic coronary artery perfusion of the myocardium.

**Afterload** is defined as the force opposing ventricular contraction, either as the stress imposed on the ventricular wall during systole, or as the vascular (aortic and systemic arterial) impedance to the ejection of the stroke volume. Wall stress increases with the pressure generated and the radius of the chamber, and is inversely related to wall thickness. A thinned, dilated failing ventricle has much higher wall stress than a hypertrophied ventricle, the compensatory thickening reducing wall tension.

The actions of the major groups of drugs are summarized in Table 1. The table describes the primary action of the drug. It should be noted that the primary action of some drugs will trigger a homeostatic physiological response; for example, the direct pressor effect of phenylephrine triggers a rate-depressor reflex which slows the heart rate.

### Preload

**Influencing the circulating volume**

The circulating volume and blood pressure are influenced fundamentally by the renin-angiotensin system. The juxtaglomerular apparatus in the macula densa of the kidney cleaves renin from pro-renin and stores it. Renin is

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**Key points**

- CVS drugs may influence preload, contractility, heart rate and afterload
- The final common pathway for many drugs is the G-protein system
- Angiotensin II receptor antagonists are potent antihypertensives
- Potassium channel blockers cause smooth muscle relaxation
- The Vaughan-Williams classification is still clinically useful
released in response to decreased renal perfusion pressure, lowered tubular sodium concentrations or by β-adrenoceptor stimulation. Renin acts on angiotensinogen to form angiotensin I which, in turn, is hydrolysed to angiotensin II by angiotensin I converting enzyme (ACE) present in the lungs and kidney. Angiotensin II is a potent vasoconstrictor acting directly on pre-capillary arterioles and indirectly by stimulating the sympathetic nervous system. It triggers aldosterone release by the adrenal cortex which enhances sodium absorption at the distal convoluted tubule. Angiotensin II receptors are distributed through vascular smooth muscle, the adrenal cortex, heart, brain and kidney.

ACE inhibitors (e.g. ramipril) are potent antihypertensives, acting at multiple sites in this pathway. They reduce ACE mediated bradykinin (a vasodilator) breakdown. Side effects include cough, rash (angioneurotic), postural hypotension and hyperkalaemia. Their use is hazardous in conditions of diminished renal perfusion, e.g. renal artery stenosis and the postoperative, hypovolaemic patient. Some patients have a poor response to ACE inhibitors which may be due to production of angiotensin II by other synthetic pathways.

An alternative approach to this has been the development of effective angiotensin II receptor blockers. Losartan and candesartan display non-competitive binding to the receptor. Both drugs are well absorbed orally, metabolised to active metabolites and do not accumulate. They are as efficacious as ACE inhibitors in hypertension and may have some reno-protective effects. They are additive in effect with thiazides and β-blockers. The therapeutic response is gradual and there is no postural hypotension.

Diuretics will be covered by a later article in this series. In brief, the ‘loop’ diuretics, e.g. frusemide, inhibit the Na+/K+/Cl– ion co-transport system in the ascending Loop of Henle and are used to offload fluid rapidly in heart failure. The thiazide diuretics act as sodium and calcium ion co-transport inhibitors at the ascending limb of the Loop of Henle and distal convoluted tubule leading to sodium, chloride and bicarbonate ion loss. Bendrofluazide produces a mild diuretic and antihypertensive effect.

**Contractility**

**Myocardial function**

Calcium enters the cell through voltage-dependent channels in the sarcoplasma reticum during depolarisation. It binds with troponin C, which cancels tropomyosin’s inhibitory action on actin and myosin binding. The myosin heads contract and the fibres slide on each other causing muscle contraction. The Ca2+ is immediately resequestered in the sarcoplasma reticum. These processes are critically dependent on cAMP.

**Matching oxygen supply with demand**

Organic nitrates maximally increase venous capacitance at very low doses. Increasing doses progressively dilate both conductance and resistance arterioles. All nitrogen-oxide containing substances (nitroprusside, nitroso compounds, nitrates) enter the smooth muscle cell and are converted to NO or S-nitrosothiols which enhance cGMP production. This stimulates a cGMP-dependent protein kinase which dephosphorylates the myosin light chain, causing relaxation. These drugs also act on the pulmonary circulation. Sulphydryl (–SH) groups are required to form NO. Excessive nitrate therapy depletes these –SH stores, leading to therapeutic tolerance. Wall tension is reduced, afterload is decreased and coronary flow is enhanced with reduced oxygen demand.

Nicorandil, a potassium channel activator, is a nicotinamide-organic nitrate hybrid. Nicorandil activates an ATP-sensitive K+ channel that remains closed in the normal heart. As ATP concentrations fall in the failing heart, it is activated. This efflux promotes cellular hyperpolarisation, reducing Ca2+ availability for contraction coupling. This indirectly relaxes smooth muscle and reduces myocardial workload. An oral preparation with good bioavailability, it is efficacious in chronic angina. It is not arrhythmogenic.
However, it does destabilise patients with left ventricular failure and low filling pressures.

Milrinone is an intravenous phosphodiesterase III inhibitor, which increases cAMP by decreasing breakdown, with cardiac and peripheral vessel effects. It enhances right ventricular contractility, markedly reduces pre-load and reduces pulmonary artery vasoconstriction. Efficacious in right ventricular failure and pulmonary hypertension, it requires invasive monitoring for safe use. It is often used in tandem with an α-agonist, e.g. noradrenaline, to offset the wide-spread vasodilation it causes.

Caffeine and theophyllines are non-specific PDE inhibitors, so have pro-inotropc activity, albeit with a wider side-effect profile.

β-Adrenoceptor blockers are used to control hypertension and heart failure, tachydysrhythmias and angina. Esmolol is an intravenous cardio-selective competitive antagonist at the β₁-adrenoceptor. Its short duration of action (t½ = 9 min) relates to its inactivation by hydrolysis by red blood cell esterases. Its principal role is acute control of peri-operative hypertension and tachycardia, including supraventricular tachycardia in cardiac, thyroid and neurosurgery, and for controlling hypertension on tracheal extubation.

Heart rate
Anti-arrhythmics

The Vaughan Williams classification is based on the mechanism of drug action, and can be readily understood on the simplified action potential shown in Figure 1.

Class I
Sodium channel blockers divided into three subgroups – A, B and C. Group A depresses phase 0; slows conduction (moderate); prolongs repolarisation, e.g. disopyramide. Group B shortens repolarisation (reducing re-entry phenomena through refractory tissue); minimal phase 0 depression, e.g. lignocaine. Group C depresses phase 0 markedly, slows conduction markedly, mild effect on repolarisation, e.g. flecainide.

Flecainide is a fluorinated derivative of procainamide. It blocks the fast inward sodium current, reducing automaticity. However, it interacts variously with many cardiac drugs including: increasing plasma concentration (amiodarone), synergistically depressing myocardial function (verapamil) or enhancing QT prolongation (tricyclics). It worsens heart failure, causes dose-dependent widening of QRS complexes in normal hearts and increases mortality in post-myocardial infarction patients. Its use is limited to cardioverting acute atrial fibrillation to sinus rhythm, in structurally normal hearts. Propafenone is a new Class Ic drug which may be less toxic.

Class II
β-Adrenoceptor blockers, e.g. propanolol, act on phase 4 to increase the refractory period and decrease automaticity.

Class III
These prolong depolarisation, e.g. amiodarone. They prolong the action potential duration (phase 2/3) prolonging refractoriness. They may prolong further the already delayed refractory pathway in a re-entry circuit, halting re-entry phenomena and, therefore, ventricular extra-systoles.

Class IV
Covers the calcium channel blockers, e.g. verapamil. They slow the action potential upstroke in the SA and AV nodes, and prolong the plateau of phase 2 in atrial, Purkinje and ventricular tissue.

Adenosine stimulates cardiac adenosine type-1 receptors enhancing K⁺ conduction and hyperpolarising atrial and AV node cells. It is useful in the treatment of supraventricular tachycardias, but is ineffective in atrial fibrillation and ventricular tachycardias.

Digitalis binds to the α-subunit of the Na⁺/K⁺-ATPase which is up-regulated in heart failure. It blocks the ATP synthesis required in phase IV to extrude sodium from intracellular stores. Potassium is lost, and enhanced concentrations of intracellular calcium are available to the contractile proteins. It increases arterial and venous tone in the fit subject, but reduces them in the heart.

Fig. 1 The action potential of a ventricular myofibril (solid line) with ECG superimposed (dotted line). Phase 4 (fastest in SA node): gradual leak of positive ions towards threshold. Phase 0: as the resting membrane potential reaches –90 mV, rapid depolarisation caused by fast influx of Na⁺ ions. +30 mV achieved. Phase 1: K⁺ channel opening, initiating repolarisation. Phase 2: slow opening Ca²⁺ channels, determining the duration of the action potential (plateau phase/absolute refractory phase). Phase 3: determined by overwhelming K⁺ outflow, coupled with Na⁺ outflow. This is the relative refractory phase. If delayed, can facilitate re-entry phenomena. Phase 4: progressively less leak K⁺ ions outwards, progressively faster inward Na⁺/Ca²⁺ leak.
failure patient. It renders the resting potential less negative, so spontaneous depolarisation is achieved more quickly. Conduction through the AV node and Purkinje system is slowed and the ventricular refractory period is enhanced.

**Afterload**
**Smooth muscle relaxation and constriction**

This effect is primarily mediated through adrenergic receptor function in the peripheral circulation. However, adenosine, dopamine and angiotensin II receptors also play a role. The most relevant development has been the identification of the common pathways by which they exert their functions, the G-proteins and the message cascade of intracellular activation/inhibition.

**Adrenergic receptor function**

Adrenoceptors are activated by locally released and circulating catecholamines. Arterioles and veins contain $\alpha_1$ and $\alpha_2$ receptors activation of which causes vasoconstriction. Vessels in skeletal muscle beds contain $\beta_2$ receptors which cause vasodilation.

The heart contains $\beta_1$ and $\beta_2$ receptors. The atrial ratio is 60:40 and ventricular 85:15. They are pro-chronotropic and pro-inotropic. $\beta_2$-Receptors are important in maintaining rate and contractility in chronic heart failure. The atria contain presynaptic $\alpha_2$ receptors which inhibit noradrenaline release.

The sequence of events following ligand binding of these receptors is summarised in Figure 2A,B.

Adrenaline ($\beta_1$, $\beta_2$), adenosine ($A_2$) and dopamine ($D_1$) receptors act via G-S (stimulatory) protein (Fig. 2A), increasing cytosolic adenylyl-cyclase activity, converting ATP to cAMP, activating protein kinase C, enhancing protein phosphorylation. This enhances vasoconstriction and tachycardia and increases myocardial contractility. Phosphodiesterase inhibitors inhibit the breakdown of cAMP to $5^\prime$AMP, its inactivation step.

Adrenaline ($\alpha_2$), dopamine ($D_2$) and angiotensin II receptors act via G-I (inhibitory) protein (Fig. 2A), reducing adenyl cyclase activity, causing vasodilation.

$\alpha_1$-Receptors act via a different mechanism (Fig. 2B). This G-P protein activates phospholipase C, which cleaves phosphoinositol 4,5-bisphosphate ($PIP_2$) to di-acylglycerol (DAG) and inositol trisphosphate ($IP_3$). DAG activates intracellular protein kinase C, releases arachidonic acid (enhancing prostaglandin synthesis and increasing cAMP) and directly increases cGMP synthesis. $IP_3$ releases intracellular $Ca^{2+}$ from stores, which act as a third messenger via, for example, calmodulin.

A systemic approach to the action of cardiovascular drugs allows clinicians to safely incorporate new drugs into their practice.

**Key references**


See multiple-choice questions 3–5.