Pharmacological modulation of cardiac function and blood vessel calibre

Christopher P Hebbes

Abstract

Inadequate end organ perfusion and tissue hypoxia is an end point of many disease processes in critical illness. Maintenance of blood flow and hence tissue oxygenation is critical to the management of intensive care patients. End organ blood flow is determined by a balance of myocardial factors (stroke volume and heart rate) and vascular factors (vasodilation and constriction). Global blood flow is determined by a balance of neurohormonal factors, with local autoregulation ultimately determining regional flow. Pharmacological manipulation of both the myocardium and vasculature at the level of the autonomic nervous system (via α or β adrenoceptors), myocardium (e.g. calcium sensitization via levosimendan), or locally (e.g. via sympathectomy) is commonly used in anaesthesia to mitigate the effects of critical illness and to maintain organ perfusion, either through increasing vascular tone or cardiac output. This article considers the global control of the system through to local and regional regulation of blood flow, and how the system may be manipulated at every stage.

Keywords Antiarrhythmics; autonomic; inotropes; shock; vasodilators; vasopressors

Royal College of Anaesthetists CPD Matrix: 1A01,1A02,2C03,2C04

Learning objectives

After reading this article, you should be able to:

- list pharmacological targets in the autonomic nervous system for manipulating cardiovascular function
- list pharmacological targets in the myocardium and blood vessels for manipulating cardiovascular function
- describe local control of the myocardium and vessel calibre
- describe neurologic control of the myocardium and vessel calibre
- discuss the evidence for vasopressors in septic shock

Neurohormonal control of the cardiovascular system

Drugs acting on the cardiovascular system are commonly used in anaesthesia and intensive care to mitigate the effects of critical illness and anaesthesia on blood pressure and to maintain organ perfusion, either through modulating vascular tone or cardiac output. In general, these drugs act via the autonomic nervous system, via local mediators, or via novel mechanisms (such as levosimendin mediated calcium sensitization). This level of control at the endocrine, paracrine or neurocrine level facilitates a coordinated whole organism response to stressors, and enables local tissue demands to be met.

Cardiac contraction

In response to the spontaneous depolarization of the sinoatrial (SA) node in the right atrium, a wave of depolarization crosses the atria to the atrioventricular (AV) node. Following a variable AV delay, this depolarizing wave is conducted through the His-Purkinje system into the ventricles which then undergo subsequent depolarization and contraction. The myocytes are then refractory, insensitive to further depolarizing stimuli until repolarization has occurred, governed by the sodium–potassium ATP-ase pump.

Following depolarization of the ventricular or atrial myocytes, L-type calcium channels allow a calcium influx, which stimulates further calcium release from intracellular sarcoplasmic reticular stores. Intracellular calcium also increases by active transportation mechanisms.

The final step of excitation contraction coupling is mediated by interaction between a troponin–actin complex and myosin. The intracellular calcium binds to troponin C, exposing a myosin-binding site on the actin filaments. This enables myosin to bind to the actin filament, and, with the hydrolysis of adenosine triphosphate (ATP), the myosin head undergoes a power stroke, and the sequence repeats. Therefore, the determinants of contraction are membrane polarity (determined by the balance of intra- and extracellular cations and anions), and intracellular calcium concentration. A detailed discussion of contraction–conduction coupling is beyond the scope of this paper; for a more detailed discussion of the mechanics of cardiac muscle excitation, see Levick.[1]

Autonomic nervous system

The autonomic nervous system provides overarching control of homoeostasis, either through direct innervation of organs and ganglia via adrenergic and cholinergic nerve fibres, or through the endocrine secretion of catecholamines from the adrenal glands. The autonomic nervous system is a target for drugs affecting both cardiac output and vasomotor tone. For a detailed explanation of the role of the autonomic nervous system, see Rang, Dale and Ritter.[2]

The autonomic nervous system is divided into the parasympathetic and sympathetic branches. Under basal conditions, the parasympathetic nervous system predominates and favours a resting state.

The myocardium is innervated by both the parasympathetic and sympathetic nervous systems. The parasympathetic innervation is via the vagus nerve, the right vagus to the SA node, and the left to the AV node and atria. Sympathetic efferent fibres pass

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to the atria, ventricles and conducting system from the cervical ganglia, originating from T1–T4.

The SA and AV nodes, atria, and ventricles express β_1 adrenoceptors, G-protein coupled receptors (GPCRs), coupled to G_s, and associated with an increase in adenylate cyclase activity. The resultant increase in cyclic adenosine monophosphate (cAMP) leads to protein kinase A (PKA) activation (see Figure 1). This leads to the phosphorylation of ion channels, enhanced spontaneous depolarization in the pacemaker cells, and increased myocardial sensitivity to depolarization. Phosphorylation also enhances Calcium channel activity. This therefore increases rate, force, and automaticity of contraction due to a raised intracellular calcium, resultant depolarization and enhanced actin–myosin coupling.

The myocardium, with the exception of the ventricles expresses M_2 muscarinic cholinergic receptors, coupled to G_i, therefore causing inhibition of adenylate cyclase, a reduction in cAMP, reduced intracellular calcium and potassium efflux. This favours hyperpolarization and reduced excitability. Therefore, this promotes bradycardia, low cardiac output, reduced automaticity, dronotropy, inotropy and atrioventricular block. Importantly, cholinergics have no effect on the ventricles as they do not express M_2 receptors.

The vasculature is also innervated by the sympathetic nervous system, and express β_2 and α adrenoceptors.

Drugs affecting cardiac function (Table 1)

Cardiac output is the product of heart rate and stroke volume, and may therefore be affected by either of these variables. Within the myocardium, heart rate is effectively determined by the membrane potential and hence electrical excitability of the pacemaker cells, and to a lesser degree the conducting system and myocardium. The SA node is the endogenous pacemaker, and undergoes spontaneous depolarization. The rate of this depolarization is a determinant of the underlying sinus rate, whereas the membrane potential of the conducting system determines the rate of transmission to the ventricles and any degree of conduction block. *Chronotropes* affect heart rate by pharmacological manipulation of this system, either by directly or indirectly affecting potassium or calcium channels or ATPases. *Dronotropes* affect the speed of conduction within the myocardium and conducting system.

The stroke volume is determined by the preload, afterload and contractility, which are determined by fluid volume loading, vasomotor tone, and by the excitation–contraction coupling within the myocardium. *Inotropes* increase the force of contraction for a give degree of preload and myocardial filling, whereas *lusitropes* affect the degree of myocardial relaxation during diastole, permitting greater diastolic filling and hence stroke volume.

All of the above factors are part of the complex interplay to determine the cardiac output. For a detailed review of myocardial physiology, see Levick.[1]

Drugs targeted towards the autonomic nervous system

The major autonomic effects are mediated through the β_1 and α adrenoceptors (Table 2). β_1 adrenoceptors are found throughout the myocardium, conducting system, pacemakers, atria and ventricles. α_1 adrenoceptors have a widespread distribution in vasculature, whereas α_2 adrenoceptors are located on prejunctional neurones and inhibit the release of noradrenaline. β_1 adrenoceptors cause positive inotropy, chronotropy and

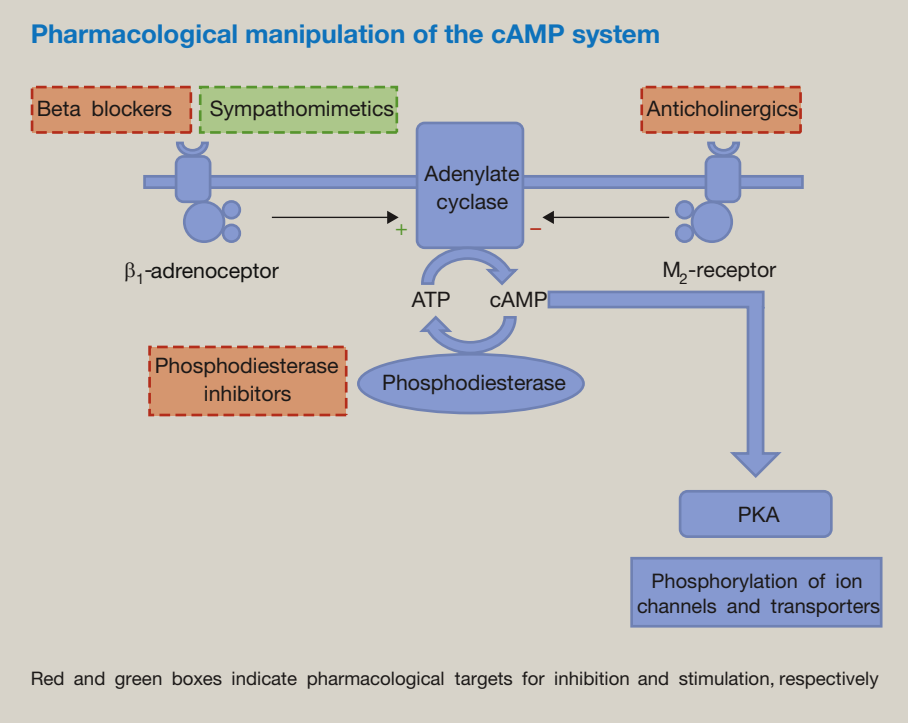

Figure 1