Cardiovascular failure, inotropes and vasopressors

Introduction

Cardiovascular failure ('shock') means that tissue perfusion is inadequate to meet metabolic demands for oxygen and nutrients. If uncorrected this can lead to irreversible tissue hypoxia and cell death. Cardiovascular failure is a common indication for admission to the critical care unit. The aim of treatment is to support tissue perfusion and oxygen delivery which can be achieved through the use of vasoactive drugs (inotropes and vasopressors).

Inotropes increase cardiac contractility and cardiac output while vasopressors cause vasoconstriction which increases blood pressure. Some vasoactive drugs are potent and have deleterious side effects, so they must only be used on critical care units where appropriate monitoring is available. Advances in therapeutics and monitoring have contributed to the increasingly aggressive treatment of cardiovascular failure and junior doctors may regularly encounter patients treated with vasoactive drugs. This article provides a practical overview of vasoactive drugs and cautions against their use outside the critical care setting.

Cardiovascular physiology

The main function of the cardiovascular system is to deliver oxygen and nutrients to cells to meet their metabolic requirements and remove waste products. The use of vasoactive drugs is aimed at maintaining this function therefore a thorough understanding of cardiovascular physiology and pharmacology is essential for safe and appropriate use of these drugs. *Table 1* summarizes the key physiological parameters.

Preload, afterload and contractility determine the stroke volume. Preload is the tension in the ventricular wall during diastole as the heart fills with blood resulting in stretching of cardiac muscle fibres. Stretching the fibres increases the force of contraction during the subsequent systole (Frank–Starling mechanism of the heart).

Afterload is the tension in the ventricular wall required to eject blood into the aorta. This will vary depending on the volume of the ventricle, the thickness of the wall, increased systemic vascular resistance and the presence of conditions that obstruct outflow (e.g. aortic stenosis).

Contractility is the intrinsic ability of the heart muscle to contract for a particular preload and afterload. It is predominantly affected by extrinsic factors summarized in *Table 2*.

Oxygen delivery

Adequate oxygen delivery is dependent on both the cardiac output and the arterial oxygen content. Most oxygen transported in the blood is bound to haemoglobin. A gram of fully-saturated haemoglobin can carry 1.34 ml of oxygen. Oxygen will also be dissolved in the plasma but the amount is negligible at normal atmospheric pressures and therefore disregarded. Therefore the arterial oxygen content and oxygen delivery can be calculated using the formulae:

Table 1. Definitions of key parameters in cardiovascular physiology

Parameter (units)	Definition
Heart rate (beats/min)	Number of ventricular contractions per unit time
Stroke volume (ml)	Volume of blood ejected from the left ventricle with each contraction
Cardiac output (litre/min)	Volume of blood ejected from the left ventricle over unit time
	Cardiac output = stroke volume x heart rate
Stroke index (litre/m^2)	Stroke volume related to the size of the individual
	Stroke index = stroke volume/body surface area
Cardiac index (litre/min/m^2)	Cardiac output related to the size of the individual
	Cardiac index = cardiac output/body surface area
Systemic vascular resistance (Dyne s/cm^5)	Resistance to blood flow in the systemic circulation
Mean arterial pressure (mmHg)	Mean blood pressure across the cardiac cycle
	Mean arterial pressure = diastolic pressure + (pulse pressure/3) and = cardiac output x systemic vascular resistance
Pulse pressure (mmHg)	Difference in pressure during systole and diastole
	Pulse pressure = systolic pressure – diastolic pressure

Table 2. Extrinsic factors affecting myocardial contractility

Decreased contractility	Acidosis and alkalosis
	Cardiac disease (e.g. ischaemic heart disease, cardiomyopathy)
	Drugs – β blockers (e.g. metoprolol), calcium-channel antagonists (e.g. verapamil)
	Electrolyte disturbance, e.g. hyperkalaemia, hypocalcaemia
	Hypoxaemia and hypercapnia
	Parasympathetic nervous system stimulation
Increased contractility	Catecholamines (e.g. adrenaline, dopamine)
	Inotropic drugs
	Sympathetic nervous system stimulation (e.g. sepsis, surgical stress response, exercise)

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Oxygen content = SaO_2 x 1.34 x [Hb]
and
Oxygen delivery = oxygen content x cardiac output

Where SaO_2= percentage oxygen saturation, 1.34 = oxygen content of 1 g saturated haemoglobin, [Hb] = concentration of haemoglobin (g/litre).

As can be seen from the above formulae, optimization of oxygen saturation and cardiac output improves oxygen delivery. Excessive transfusion to supranormal haemoglobin concentrations will increase blood viscosity and cardiac workload. Inotropes and vasopressors are an effective and controllable way of maintaining tissue perfusion and oxygen delivery.

Cardiovascular pharmacology and vasoactive drugs

The most commonly used inotropes and vasopressors are catecholamines. The naturally occurring catecholamines (dopamine, noradrenaline, adrenaline) act as neurotransmitters and hormones; their synthetic pathway is shown in *Figure 1*. Dobutamine and dopexamine are synthetic catecholamines (having a similar chemical structure to the endogenous catecholamines). Catecholamines act mainly on adrenergic receptors, which are a family of G protein-coupled receptors that span the extracellular membrane. The action of catecholamines at these receptors is explained in *Figure 2*. Catecholamines are rapidly inactivated by re-uptake at the presynaptic nerve and so have a short half-life. Dopamine can activate both dopamine receptors (also G protein-coupled) as well as adrenergic receptors.

The physiological effect of stimulation depends on the catecholamine released and the receptor subtype and location. The important receptors in the cardiovascular system are the α1, β1 and β2 adrenergic receptors. The effects on these are summarized in *Table 3* and *Figure 3*. To optimize cardiovascular function drugs are used that act on receptors which when stimulated improve cardiac function and vascular smooth muscle tone.

Different catecholamines have varying affinity for the adrenergic receptor subtypes and therefore produce different effects (*Table 4*). Not all of these effects are desirable, so patients need to be selected carefully and the dose of drug titrated cautiously.

Figure 1. Catecholamine synthesis.

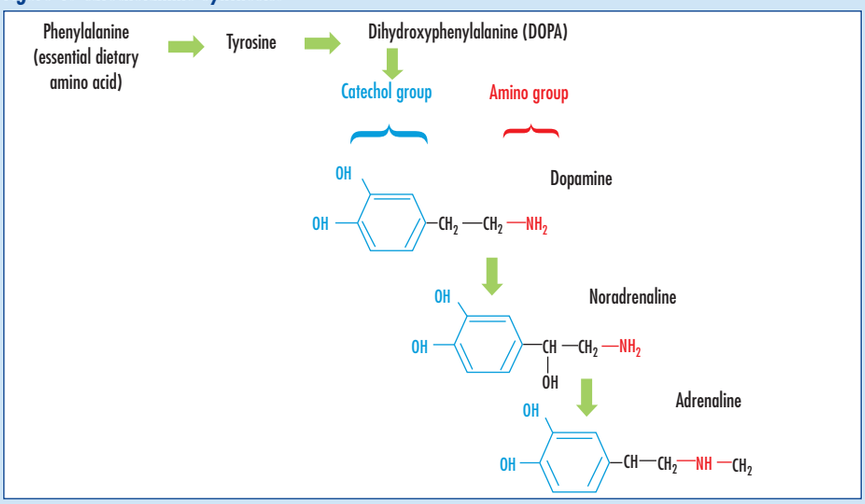


Table 3. Adrenergic receptors and the cardiovascular system

Receptor	Location	Effect of stimulation
α1 adrenergic	Vascular smooth muscle (peripheral, renal and coronary circulation)	Vasoconstriction (increasing systemic vascular resistance)
β1 adrenergic	Heart	Increased heart rate and increased contractility (increasing cardiac output)
β2 adrenergic	Vascular smooth muscle (peripheral and renal circulation)	Vasodilatation (reducing systemic vascular resistance)

Who needs vasoactive drugs?

Not all patients with cardiovascular failure will need treatment with vasoactive drugs. Correction of fluid balance can improve cardiovascular parameters, increasing perfusion and oxygen delivery. However, vasoactive drugs may be considered if there are continuing signs of inadequate tissue perfusion or oxygen delivery despite appropriate fluid resuscitation.

In clinical practice mean arterial blood pressure and heart rate are measured because this can be done easily, but the presence of tachycardia and hypotension are often late signs. Blood pressure and

Figure 2. Diagram of an adrenergic receptor. This has seven transmembrane domains. Catecholamine binds to the receptor extracellularly and causes a change in the intracellular structure that enables it to activate a G protein. The activated G protein triggers a secondary messenger cascade. For adrenergic receptors this is most often through adenylate cyclase and cyclic AMP. The other principal signalling pathway is through phospholipase and inositol triphosphate and diacylglycerol.

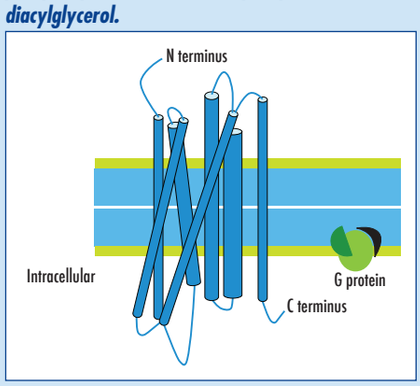
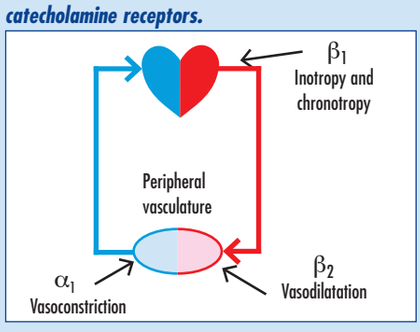


Figure 3. Locations and effect of stimulation of catecholamine receptors.



heart rate can give an indication of cardiovascular status but there are many other parameters that affect cardiac output and oxygen delivery (*Table 1*).

Clinical assessment facilitates recognition of subtle indicators of poor perfusion. The exact findings will vary depending on the underlying cause of shock. Inadequate perfusion will impact on the function of vital organs, for example reduced renal perfusion will reduce renal output and poor brain perfusion may manifest as confusion. *Table 5* summarizes some of the key findings in a compromised circulation and provides a checklist for examination.

Once patients with cardiovascular failure (shock) are identified it is important to determine the underlying cause to enable treatment. Shock is commonly classified by its underlying mechanism which is summarized in *Table 6*. Inotropes are used to improve contractility and cardiac output. Vasopressors are used where the problem is a low systemic vascular resistance.

Practicalities

Catecholamines are given as continuous infusions because of their short half-life. Further their effects on the cardiovascular system are potent and dosing must be carefully monitored and adjusted. This is only possible with an infusion. Inotropes and vasopressors must be administered via central access because there is a risk of skin necrosis if they extravasate. Invasive monitoring is required because rapid changes in blood pressure and arrhythmias can occur during the administration of these drugs. Therefore beat-to-beat monitoring of arterial pressure via an arterial line is mandatory. Other invasive monitoring systems can be used, such as oesophageal Doppler, LiDCO and PiCCO systems, which enable measurement of cardiovascular parameters to calculate cardiac output and stroke volume.

Table 4. Receptor actions of catecholamines

Drug	Receptor affinity	Action	Dose range (μg/kg/min)	Side effects
Noradrenaline	Mainly α1 agonist, some β1 agonist action	Vasoconstriction increasing systemic vascular resistance	0.03–0.2	Reduced renal perfusion as a result of vasoconstriction, increased afterload will reduce stroke volume and increase myocardial oxygen demand
Adrenaline	Low doses: β1 agonist	Increased heart rate, stroke volume and cardiac output	0.01–0.15*	Tachycardia and tachyarrhythmia, increased myocardial oxygen demand
	High doses: α1 agonist	Vasoconstriction at higher doses increasing systemic vascular resistance	0.01–0.15*	High concentrations can cause reduced cardiac output
Dobutamine	β1 agonist	Increased heart rate, increased cardiac output	2.5–25	Tachyarrhythmia, increased myocardial oxygen consumption
	β2 agonist	Vasodilatation and reduced systemic vascular resistance	2.5–25	Risk of hypotension
Dopamine	Low dose: dopamine receptor agonist	Vasodilatation of capillary beds, reduced systemic vascular resistance and increased cardiac output	1–3	Risk of tachyarrhythmia
	Medium dose: β1 agonist	Increases contractility, stroke volume and cardiac output	3–10	Previously used at low ('renal') doses to maintain renal perfusion and function
	High dose: α1 agonist	Vasoconstriction increasing afterload, peripheral resistance and mean arterial pressure	>10	No longer used as any benefit on renal outcome is caused by the increased cardiac output

* there is no strict cut off between high and low dose so dose range applies to both

Table 5. Evidence of inadequate tissue perfusion

Oliguria or anuria
Confusion or agitation
Cool and clammy skin (although skin warm and sweaty in sepsis)
Weak or thready pulses
Slow capillary refill time
Tachypnoea
Tachycardia
Hypotension
Metabolic acidosis (negative base excess)

Table 6. Classification and mechanisms of shock

	Mechanism	Causes
Cardiogenic	Pump failure: ↓ contractility, ↓ cardiac output	Myocardial infarction, arrhythmias, decompensated cardiac failure
Hypovolaemia	Fluid loss: ↓ preload, ↓ stroke volume and ↓cardiac output	Haemorrhage, dehydration
Sepsis	Peripheral vasodilatation, extravasation of fluid: ↓ systemic vascular resistance; normal or increased cardiac output with reduced capillary blood flow as a result of microcirculatory shunt; mitochondrial dysfunction with reduced oxygen extraction	Bacterial infection, e.g. *Streptococcus pneumoniae*, *Escherichia coli*
Neurogenic	Peripheral vasodilatation: ↓ systemic vascular resistance	Spinal cord transection, brainstem injury
Anaphylaxis	Vasodilatation and pump failure: ↓ systemic vascular resistance and ↓ cardiac output	Drug or food allergens

Table 7. Non-catecholamine vasoactive drugs

Drug	Mechanism	Action
Enoximone, milrinone	Phosphodiesterase III (PDE III) inhibitor, prevent hydrolysis of intracellular cyclic AMP, augmenting its effects. Many isoenzymes of phosphodiesterase – PDE III is the target for inotropic actions	Increased cardiac contractility and stroke volume, vasodilatation
Levosimendan	Calcium sensitizer. Increases the sensitivity of myocardial troponin to intracellular calcium, possible inhibition of PDE III	Increased cardiac contractility without increasing myocardial oxygen demand, effect on mortality unclear
Vasopressin	Endogenous hormone, also called antidiuretic hormone, V1 receptor activity in vascular smooth muscle increasing intracellular calcium	Vasoconstriction increasing systemic vascular resistance and blood pressure

See further reading for more information

For all these reasons treatment with inotropes and vasopressors necessitates care by an expert on a high dependency unit.

It is important to regularly re-assess fluid balance. Patients should be adequately fluid resuscitated (or this should be in progress) before starting vasoactive drugs. Using inotropes or vasopressors when patients are fluid depleted can worsen perfusion.

Inotropes and vasopressors should be titrated to ensure the minimum amount of drug is used to maintain adequate tissue perfusion without causing adverse effects. The aim is not to maintain a specific blood pressure but to achieve satisfactory end-organ perfusion, which can be assessed clinically or with measured markers of organ perfusion.

Vasoactive drugs are only supportive: they do not reverse the underlying cause of cardiovascular failure which must be addressed. Prolonged treatment with vasoactive drugs is undesirable because overstimulation of receptors will also result in tachyphylaxis, i.e. tolerance develops as a result of downregulation of membrane receptors, and cardiac oxygen demands increase and may induce ischaemia and damage to cardiac myocytes.

Dose ranges for common inotropes and vasopressors are listed in *Table 4*. However, given the potency of the drugs, infusions should be started cautiously and titrated to use the lowest dose for the required response.

Other vasoactive drugs

There are a number of other vasoactive drugs that do not act directly on catecholamine receptors. These are used in clinical practice but none are considered first line and there is no definite evidence that they improve outcomes. *Table 7* summarizes the mechanism and actions of some more commonly used drugs of this type.

Conclusions

Inotropes and vasopressors are often used in the management of shock. Doctors working in the acute setting need knowledge of the pathophysiology of shock and the pharmacology of vasoactive drugs to enable them to identify and refer patients who would benefit from their use on critical care. There is no definitive evidence as to which vasoactive drug should be first line for a particular cause of shock, so drug choice varies between different critical care units. Understanding the mechanism of action and principles of management when using these drugs can guide clinical practice. BJHM

Conflict of interest: none.

Further reading

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KEY POINTS

- Cardiovascular failure and shock occur when tissue oxygen delivery is inadequate to meet tissue oxygen demand.
- Early recognition of the signs of shock is difficult.
- Early treatment of shock is crucial to avoid irreversible cellular hypoxia.
- Cardiac output and arterial oxygen content must be optimized before commencing vasoactive therapies.
- Inotropes increase myocardial contraction and cardiac output.
- Vasopressors increase systemic vascular resistance.
- Patients on inotropes and vasopressors should be managed on a critical care unit.

TOP TIPS

- Regularly reassess patients for improvement in cardiovascular parameters and side effects of vasoactive drugs.
- Monitor biochemistry for derangement in electrolytes and glucose. Adrenaline in particular can cause hyperglycaemia, increased lactate levels and metabolic acidosis.
- Check local guidelines – different critical care units will have their own preferred drugs, preparations and dose regimens.
- Check patient drug history for potential drug interactions, for example tricyclic antidepressants and monoamine oxidase inhibitors can produce exaggerated responses to catecholamines.