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REVIEW

Use of inotropes and vasopressor agents in critically ill patients

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Inotropes and vasopressors are biologically and clinically important compounds that originate from different pharmacological groups and act at some of the most fundamental receptor and signal transduction systems in the body. More than 20 such agents are in common clinical use, yet few reviews of their pharmacology exist outside of physiology and pharmacology textbooks. Despite widespread use in critically ill patients, understanding of the clinical effects of these drugs in pathological states is poor. The purpose of this article is to describe the pharmacology and clinical applications of inotropic and vasopressor agents in critically ill patients.

LINKED ARTICLES
This article is commented on by Bracht *et al.*, pp. 2009–2011 and De Backer and Scolletta, pp. 2012–2014 of this issue. To view Bracht *et al.* visit http://dx.doi.org/10.1111/j.1476-5381.2011.01776.x and to view De Backer and Scolletta visit http://dx.doi.org/10.1111/j.1476-5381.2011.01746.x

Abbreviations
$[Ca^{2+}]_i$, Intracellular calcium concentration; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; CPR, cardiopulmonary resuscitation; DO_2, systemic oxygen delivery; GPCR, G-protein coupled receptor; GTP/GDP, guanosine triphosphate/diphosphate; PKA/PKC, protein kinase A/C; PLC, phospholipase C; SvO_2, mixed/central venous oxygen saturation; TNF-α, tumour necrosis factor alpha; VO_2, oxygen consumption

Introduction

Inotropes are agents administered to increase myocardial contractility whereas vasopressor agents are administered to increase vascular tone. The use of these potent agents is largely confined to critically ill patients with profound haemodynamic impairment such that tissue blood flow is not sufficient to meet metabolic requirements. Examples include patients with severe heart failure and septic or cardiogenic shock, as well as patients undergoing major surgery and victims of major trauma. They are generally administered via a large central vein and, in some specific situations, via a peripheral vein. These agents have a diverse range of actions including metabolic and immune effects, many of which are poorly understood. The objective of this review is to describe the underlying cardiovascular mechanisms that clinicians seek to influence through the use of inotropic agents, to describe the basic pharmacology of those drugs in common use and, finally, to explore the evidence base for specific approaches to inotrope and vasopressor therapy in clinical practice. As many of the commonly used agents exert both inotropic and vasopressor effects, the term 'inotrope' will be generally used in this review to describe agents with a spectrum of actions.

The physiological basis for the actions of inotropic agents

Myocyte excitation and contraction. Cardiac muscle fibres contract through the sliding filament mechanism. Actin and myosin filaments are propelled past each other through repeated cross-bridge linking and unlinking. Each cardiac action potential results in the opening of voltage-gated myocyte calcium channels and a rise in intracellular calcium concentration ($[Ca^{2+}]_i$). This triggers a further release of calcium from the sarcoplasmic reticulum, which accounts for around three quarters of the total increase in $[Ca^{2+}]_i$ (Levick, 2003) (Figure 1). At rest, tropomyosin blocks the actin-binding site, preventing engagement of myosin heads. Calcium ions bind to troponin C within the troponin complex, displacing tropomyosin. This exposes the actin-binding site, allowing cross-bridge formation with myosin heads. The orientation of the myosin head changes, causing filaments to slide past each other in an ATP-dependent process. At the end of the action potential, during repolarization, calcium ions are pumped back into the sarcoplasmic reticulum, allowing myocardial relaxation.

Force and rate of myocardial contraction: inotropy and chronotropy. Cardiac output is the volume of blood pumped by the

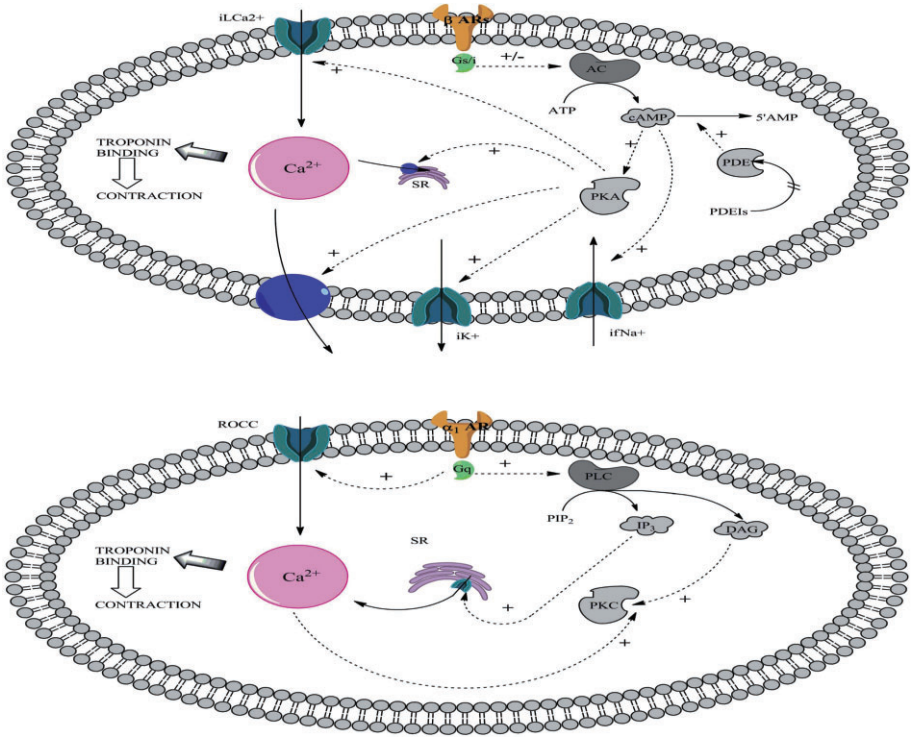

Figure 1

Intracellular mechanisms of catecholamine and PDE inhibitor (PDEI) modulation of chronotropy, dromotropy, lusitropy and inotropy. β adrenoreceptors coupled positively to adenylate cyclase via Gs increase cAMP levels and PKA activity. PDEIs inhibit cAMP breakdown, increasing levels and PKA activity. cAMP increases the open state of if(Na+) channels to increase pacemaker rate. PKA co-ordinates by activating i(K+) channels involved in repolarization. This is the cellular mechanism of chronotropy and dromotropy. PKA also increases L-type Ca2+ channel activity and enhances sarcoplasmic reticulum (SR) Ca2+ uptake and lusitropy. Increased SR Ca2+ content and L-type Ca2+ channel activation increases myocardial Ca2+ transients, resulting in greater contractile strength and inotropy. α1 adrenoceptors may also increase Ca2+ levels in a manner similar to that in vascular smooth cells, but the increase is only 10–15% of that achievable by β adrenoceptor mechanisms. α_2 adrenoceptors have not been found on cardiomyocytes.

5′AMP, 5′ adenosine monophosphate; Gs/q, G-protein signalling α subunit to which receptor is coupled; if(Na+), channel related to inward 'funny' sodium current involved in pacemaker rate; ifK+, channel related to delayed rectifier potassium current involved in repolarisation; iLCa2+, channel related to inward calcium current; IP_3, inositol 1,4,5 trisphosphate; PIP_2, phosphatidylinositol 4,5 bisphosphate.

heart each minute and is determined by the force and frequency of ventricular contraction. Increased venous return increases ventricular (and therefore myocyte) stretch in diastole, resulting in increased filament overlap and hence, an increase in the number of available calcium-binding sites. This mechanism, which is the basis of Starling's law of the heart, ensures ventricular output changes in response to changing venous return, thus, ensuring the output of the two ventricles is finely matched. The force of ventricular contraction is also affected by changes in contractility or the force of contraction for a given resting fibre length (Table 1). Inotropic agents prolong the action potential plateau duration, increasing $[Ca^{2+}]_i$, calcium release from the sarcoplasmic reticulum and hence, contractility. Myocyte stretch also affects myofilament sensitivity to $[Ca^{2+}]_i$, a mechanism exploited in the use of certain novel inotropic drugs.

Vascular tone. Resistance vessel tone, sometimes termed afterload, will influence cardiac output both directly and through complex reflexes such as the baroreceptor reflex. For a given preload and contractility, the direct effect of a decrease

Table 1

Physiological factors which determine cardiac output

Determinants of cardiac output
Myocyte stretch
Changes in venous return
Changes in plasma volume
Contractility
Sympathetic tone
Circulating catecholamines
Exogenous inotropes
Heart rate
Sympathetic and parasympathetic tone
Circulating catecholamines
Exogenous drugs with chronotropic effects

in afterload is to increase cardiac output and vice versa as afterload rises. Importantly, during periods of haemodynamic shock, loss of a number of homeostatic mechanisms may impair contractility through acidosis, reductions in coronary flow and an adverse myocardial oxygen supply–demand ratio.

Microvascular flow. The microvasculature consists of regions of the circulation containing blood vessels of diameters less than 100 μm (den Uil *et al.*, 2008). The homeostasis of these specialized areas is under myogenic, metabolic, immune and neural controls (Levick, 2003). Abnormalities of microvascular flow appear to play an important role in the pathophysiology of critical illness (De Backer *et al.*, 2004; Ince, 2005; Spanos *et al.*, 2010). Inotropic agents may influence this balance by altering both cardiac output and microvessel tone (De Backer *et al.*, 2006; Jhanji *et al.*, 2009b). Indirect effects of these drugs may also exert complex results on endothelial permeability and hence, blood volume, which is commonly reduced in critical illness (Adamson *et al.*, 1998; Waschke *et al.*, 2004).

Metabolic effects. Inotropic agents alter metabolic rate and the production of metabolically active molecules through perfusion-related, receptor and second messenger-mediated effects. These effects occur most frequently with adrenergic agonists and PDE inhibitors (PDEIs), which may increase total body oxygen consumption, peripheral insulin resistance, suppression of insulin secretion, increased fatty acid and lactate production and hyperglycaemia (Clutter *et al.*, 1980; Galster *et al.*, 1981). Importantly, hyperglycaemia may be associated with denudation of the endothelial glycocalyx and deleterious effects on the microcirculation (Lipowsky, 2005).

Immune effects. Inotropic agents have been shown to alter the state of activation of immune cells and may, therefore, have important effects on immune function, which are currently poorly understood (Oberbeck, 2006). Endothelial function is an important component of the capacity of the immune system to focus activity in specific tissue areas. Immune cell–endothelial interactions occur by shear-dependent or shear-independent mechanisms, both of which are influenced by inotropic agents. Shear-dependent mechanisms relate to flow through microvascular networks. At low flows, the probability of immune cells interacting with the endothelium increases (Lipowsky, 2005). Shear-independent mechanisms describe changes in the activation state of immune cells independent of flow. Activated cells have a greater chance of endothelial interaction at any given flow rate compared with quiescent cells.

Pharmacology of endogenous vasoactive hormones

Catecholamines. The endogenous catecholamines adrenaline, noradrenaline and dopamine are dihydroxybenzene (catechol) molecules. They act as neurotransmitters within the central and the sympathetic division of the autonomic nervous system and hormones in circulating blood. Catecholamines are synthesized in four stages within secreting nerve terminals and the adrenal enterochromaffin cells (Ganong, 2003). The first and rate-limiting step is the conversion of tyrosine to dihydroxyphenylalanine (L-DOPA) by tyrosine hydroxylase. L-DOPA is decarboxylated to dopamine, which is taken up from the cytosol into neuronal vesicles in neurones and chromaffin granules in the adrenal medulla. Here, it is converted to noradrenaline (Philipu and Matthaei, 1988). In the adrenal medulla, noradrenaline re-enters the cytosol and is converted to adrenaline.

Distribution and metabolism of endogenous catecholamines. Only 10–20% of neuronally released noradrenaline reaches the circulation (Esler *et al.*, 1990). The remainder is rapidly returned to the neurone by pre-synaptic uptake-1 or to perineuronal structures by uptake-2 transporters (Graefe and Bonisch, 1988). Reabsorbed noradrenaline is mostly recycled, but some is metabolized by MAO (Youdim *et al.*, 1988). Sixty per cent of circulating adrenaline and noradrenaline remains free within the plasma. The remainder is bound covalently to either plasma proteins (11%) or to haemoglobin in erythrocytes (El-Bahr *et al.*, 2006). There is a biphasic decay in plasma catecholamine levels, the first phase lasting around 5 min (uptake-2), and the second occurring over a month (plasma protein decay) (El-Bahr *et al.*, 2006). Catecholamine metabolism occurs slowly in erythrocytes, which also act as a storage pool (Azoui *et al.*, 1996). Uptake-1 and 2 account for 25% of adrenaline clearance from plasma (Clutter *et al.*, 1980). Circulating adrenaline and noradrenaline is subsequently metabolized, principally by COMT (Kopin, 1985). Clearance of catecholamines occurs principally in the liver and the lungs, and is increased by β-adrenoceptor-mediated mechanisms (Clutter *et al.*, 1980). The kidneys excrete catecholamines almost entirely unchanged. There is also some peripheral uptake of catecholamines, most notably in vascular smooth muscle cells and the heart (Eisenhofer, 2001). The fate of peripherally released dopamine is similar to that of noradrenaline and adrenaline.

Structure–activity relationships of catecholamines. Structural differences in catecholamines result in some differences in receptor affinity and rates of metabolism. Substitution on the amino group of the catecholamine tail reduces α-receptor affinity but increases β-receptor affinity (Henkel *et al.*, 1981; Lullman *et al.*, 2000). Furthermore, β_2 affinity is increased by the size of the substituent. The position of hydroxyl groups on the aromatic nucleus also alters adrenoceptor affinity as does hydroxyl substitution on the catecholamine tail. These latter groups are key in determining β_2 affinity. For example, dopamine and dobutamine lack side chain β-OH groups and demonstrate low affinity and intrinsic activity at β_2 adrenoceptors despite amino group substitutions (Mukherjee *et al.*, 1976; Lullman *et al.*, 2000). Metabolism by COMT is affected by the position of aromatic hydroxyl groups. Resistance to MAO is conferred by substitution of methyl groups on the amino tail with larger groups or introducing small alkyl residues (Lullman *et al.*, 2000). Alkylation of the primary amino group decreases affinity for uptake-1 (Graefe and Bonisch, 1988). Although catecholamine structure can determine the degree of adrenoceptor activation, agonists at specific adrenoceptor subtypes may still generate differing concentrations of second messengers such as cAMP, because of non-selective G-protein coupling (Xiao *et al.*, 2003). Drug–receptor interactions are also influenced by polymorphisms of adrenoceptor genes (Nakada *et al.*, 2010).

Table 2

Adrenoceptors and subtypes, their cellular signalling mechanisms and cardiovascular effects

Adrenoceptor	α		β		
Subtypes	α_1	α_2	β_1	β_2	β_3
Subclasses	α_{1A}, α_{1B}, α_{1D}	α_{2A}, α_{2B}, α_{2C}	n/a		
Principal Gα-signalling protein	$G_{q/11}$	$G_{i/o}$	G_s		
Second messengers	PLC/DAG/IP_3/ PKC	AC/cAMP/PKA (inhibits)	AC/cAMP/PKA (stimulates)		
Affinity for catecholamines	Ad = NAd	Ad > NAd	Ad < NAd	Ad > NAd	Ad = NAd
Adrenoceptor subtype in myocardium and effect of agonism	α_{1A} ↑ $[Ca^{2+}]_i$	None. Pre-synaptic α_{2A} ↓ $[Ca^{2+}]_i$	Predominantly β_1 and some β_2 ↑ $[Ca^{2+}]_i$		
Adrenoceptor subtype in vascular smooth muscle cells and effect of agonism	α_1 >> α_2 Primarily α_{1A} in arteries ↑ $[Ca^{2+}]_i$ vasoconstriction		β_2 >> β_1 β_3 role unknown ↓ $[Ca^{2+}]_i$ vasorelaxation		
Adrenoceptor subtype in vascular endothelium and effect of agonism	n/a	α_{2A} NO release vasorelaxation	β_2 NO release vasorelaxation (β_3 role unknown)		

AC, adenylate cyclase; Ad, Adrenaline; $G_{q/i/s}$, G-protein α-signalling subunit to which the relevant receptor is coupled; IP_3, inositol 1,4,5 trisphosphate; n/a, not applicable; NAd, Noradrenaline; α_1 >> α_2, implies α_1 predominates over α_2.

Table 3

Adrenoceptor distribution determines vascular responses to catecholamines

	Vessel type Arteries	Veins
Post-synaptic receptors close to synaptic junction	α_1 and β_1	α_2 and β_2
Extrajunctional post-synaptic receptors	α_2 and β_2	α_1
Coronary circulation	α_1 and α_2 in large arteries only	
	β present in small and large arteries. β_1 >> β_2.	
Cerebral circulation	Poor sympathetic innervations	
	α-adrenoceptor expression declines in smaller vessels	
	β-adrenoceptors may mediate vasodilatation	
Splanchnic,	β_2 >> β_1	
Skeletal and Pulmonary	α effects predominate over β in splanchnic circulation	
Cutaneous circulation	α_2-adrenoceptors	

Post-synaptic receptors close to the synaptic junction respond primarily to neuronal stimulation. Extrajunctional post-synaptic receptors respond primarily to hormonal stimulation or exogenous adrenergic agents. β2 >> β1 implies predominance of β2 over β1.

Function and distribution of adrenergic receptors. Adrenergic receptors are classified into α-adrenoceptors and β-adrenoceptors and further into respective subtypes (Table 2) (Alexander *et al.*, 2011). These GPCRs (Summers and McMartin, 1993; Alexander *et al.*, 2011) are susceptible to down-regulation and desensitization (Bohm *et al.*, 1997; Heck and Bylund, 1997), which is a particular problem in shock states such as sepsis (Tang *et al.*, 1998). Although widespread throughout the body, only their cardiovascular distribution is discussed in this article. Adrenoceptor location within the CVS determines the pattern of response to circulating and neuronally released adrenergic agents (Brodde and Michel, 1999; Guimaraes and Moura, 2001) (Table 3). Adrenergic receptor expression is minimal in capillaries but increases with distance from the capillary in both arterioles and venules (Furness and Marshall, 1974). The responses to catecholamines, therefore, vary across vascular beds, for example, between mesenteric beds and skeletal muscle beds (Marshall, 1982). To date no α_2 adrenoceptors have been found in the human myocardium, although other adrenoceptors are present there. Inotropy is provided predominantly by β-adrenergic mechanisms, although α_1 adrenoceptors can bring about small increases in contractility.

Function and distribution of dopaminergic receptors. There are five subtypes of dopaminergic receptors (Alexander *et al.*, 2011), classed in two groups: D_1-like (subtypes DR_1 and DR_5) and D_2-like (subtypes DR_2, DR_3 and DR_4). Whereas dopamine

may activate both dopaminergic and adrenoceptors, the former are not activated by other endogenous catecholamines (Goldberg and Rajfer, 1985; Missale *et al.*, 1998). All dopaminergic receptor subtypes have been identified in the kidney where they mediate natriuresis and diuresis (Bertorello and Aperia, 1990; Lokhandwala and Amenta, 1991). Cardiac dopaminergic receptors (DR_1 and DR_4) mostly show some inotropic effect, although less pronounced than β-adrenoceptor-mediated responses (Motomura *et al.*, 1978; Wang *et al.*, 1991; Wakita, 2007). Dopamine receptors can also be identified in the adrenal medulla, autonomic ganglia, endothelium, and the renal, mesenteric and splenic vasculature, where they are both pre- (D_2) and post-synaptic (D_1 & D_2) (Missale *et al.*, 1998). D_1 receptors are found in the media of blood vessels and cause vasodilatation. Vascular D_2 receptor activation can cause vasodilatation or constriction, depending on whether medial or adventitial (Zeng *et al.*, 2007). The overall effect of non-selective dopaminergic activation, such as what occurs during low-dose dopamine infusion, is to reduce vascular tone.

Adrenaline. Adrenaline (also known as epinephrine) is a potent agonist at all adrenoceptors resulting in profound increases in cardiac output and heart rate, mean arterial pressure, and coronary blood flow. At low doses, passive stretch of pulmonary vessels accommodates increases in cardiac output, but as the plasma concentration of adrenaline increases, it will eventually increase pulmonary vascular resistance and hence, right ventricular afterload (Aviado and Schmidt, 1957). In addition to gross cardiovascular effects, myocardial oxygen demand rises because of increased heart rate and stroke work. Splanchnic oxygen consumption and hepatosplanchnic blood flow increase in association with an increased hepatic metabolic workload (Bearn *et al.*, 1951). Metabolic effects include increased plasma glucose and lactate concentrations (Bearn *et al.*, 1951; Clutter *et al.*, 1980; Galster *et al.*, 1981). The rise in lactate is of clinical importance as lactate is utilized in critical illness as a marker of tissue hypoperfusion. However, the increase in serum lactate induced by exogenous catecholamines does not appear to be associated with harm.

Noradrenaline. Noradrenaline (also known as norepinephrine) is an inotrope and a vasopressor (Levick, 2003). Noradrenaline is often incorrectly described as a pure vasopressor because of its α-adrenoceptor agonism and weak β_2-adrenoceptor agonism (Alexander *et al.*, 2011). However, noradrenaline has clearly described effects on contractility in critical illness (Jhanji *et al.*, 2009b). The effects of noradrenaline on pulmonary vessels are similar to those of adrenaline (Aviado and Schmidt, 1957). Owing to the relative sparsity of cerebral vascular adrenoceptors, high doses of noradrenaline can be safely used to maintain cerebral perfusion pressure without significantly compromising flow in this circulation. Similarly the coronary circulation is protected to a certain extent from the vasoconstrictor effects of noradrenaline (Guimaraes and Moura, 2001). However, noradrenaline does decrease pulmonary, cutaneous, renal and splanchnic blood flow (Bearn *et al.*, 1951; Hoffbrand and Forsyth, 1973). Noradrenaline does not appear to cause an increase in serum lactate, possibly as this is a β_2-mediated effect (Day *et al.*, 1996). Compared with adrenaline, increases in plasma glucose are relatively modest and coincide with a neutral effect on splanchnic oxygen consumption in health (Bearn *et al.*, 1951).

Dopamine. Dopamine acts on both dopaminergic and adrenoceptors, giving a complex cardiovascular response profile. At low doses (up to 5 $\mu g \cdot kg \cdot min^{-1}$), primarily dopaminergic receptors are activated causing a decrease in vascular resistance and mild increase in cardiac output. At doses of 5–15 $\mu g \cdot kg \cdot min^{-1}$, β-adrenoceptor effects lead to increases in cardiac output and heart rate (Sasada and Smith, 2003). Beyond this, α-adrenoceptor effects predominate, causing an increase in vascular resistance to the extent that cardiac output may decrease. At low doses, dopamine increases renal (Mousdale *et al.*, 1988; Olsen *et al.*, 1993) and splanchnic (Sato *et al.*, 1987) blood flow. Dopamine causes a modest increase in metabolic rate, but without hyperlactataemia (Ensinger *et al.*, 1993; 1995). Neurohumoural effects of dopaminergic activation in critical illness include a suppression of prolactin, thyroid and growth hormone secretion, whereas glucocorticoid synthesis is increased (Van den Berghe and de Zegher, 1996; Bailey and Burchett, 1997); these effects may explain important immune effects of dopamine in septic patients (Beck *et al.*, 2004).

Other endogenous hormones

Vasopressin. In health, vasopressin is released from the posterior pituitary in response to osmotic, chemoreceptor and baroreceptor stimuli. In humans and most other mammals, one of the nine amino acids constituting vasopressin is arginine, although in some species, this is lysine. Vasopressin acts on vascular smooth muscle V_1 and oxytocin receptors (both G_q/PLC coupled), causing vasoconstriction. Vasopressin may also activate vascular smooth muscle V_2 receptors (G_s/adenylate cyclase/cAMP coupled) resulting in vasodilatation. Endothelial V_1, V_2 and oxytocin receptor activation results in NO-dependent vasodilatation. The importance of vascular V_2 and oxytocin receptors is unsettled though. Overall, vasopressin stimulation tends to cause constriction, but the exact response depends on the precise location of receptor and the concentration of vasopressin in the vicinity. Vasopressin modulates autonomic function through activation of brainstem V_1 receptors and can modulate endocrine status as it stimulates adrenocorticotropic hormones release via V_3 receptors (Barrett *et al.*, 2007). Exogenously administered arginine vasopressin (aVP) and lysine vasopressin differ. Tri-glycyl vasopressin, or terlipressin, is a prodrug slowly degraded by liver and kidney endo- and exopeptidases to lysine vasopressin, conferring a significantly longer duration of action after i.v. bolus than aVP. Terlipressin has a greater selectivity for vascular V_{1a} receptors but less selectivity for renal tubular V_2 receptors than aVP (Bernadich *et al.*, 1998). Terlipressin may result in pulmonary vasoconstriction (Lange *et al.*, 2007) and affect coagulation systems (Morelli *et al.*, 2009) although aVP does not.

In septic shock, the administration of exogenous aVP ($0.01–0.04\ U \cdot min^{-1}$) results in the reversal of vasodilatory shock. There are multiple mechanisms by which this may occur. Briefly, exogenously administered vasopressin may reverse a relative deficiency of the hormone seen in established sepsis. Vascular smooth muscle cation channel function and contractile machinery are affected such that vasorelaxation is

opposed. V_1 and α_1-adrenoceptor crosstalk, an amelioration of autonomic dysfunction, an increase of other endogenous vasoconstrictors and a potential effect on both NO and glucocorticoid production may also contribute to the partial restoration of vascular reactivity to catecholamines and the reversal of vasodilatation (Barrett *et al.*, 2007). The details of these mechanisms are beyond the scope of this article and may be found elsewhere (Barrett *et al.*, 2007). Research into other compounds affecting vasopressin receptor systems in sepsis is currently ongoing (Rehberg *et al.*, 2011).

Exogenous inotropes and vasopressor agents

Dobutamine. Dobutamine is a synthetic catecholamine available as a racemic mixture (Majerus *et al.*, 1989), with mixed β-adrenoceptor effects, binding in a 3:1 ratio to β_1 and β_2 adrenoceptors respectively. It also demonstrates mild α_1-adrenoceptor agonism (Ruffolo, 1987), which explains why decreases in vascular resistance do not persist at higher doses. Heart rate increases are modest and renal plasma flow is not greatly affected (Mousdale *et al.*, 1988; Olsen *et al.*, 1993). Dobutamine is widely used in the short-term treatment of severe heart failure and cardiogenic shock and is a first-line agent to increase cardiac output in septic shock, although usually in combination with a vasoconstrictor agent (Rudis *et al.*, 1996; Beale *et al.*, 2004). As dobutamine increases myocardial oxygen demand, it is used as a stressor in cardiac assessment (Patel *et al.*, 2007).

Dopexamine. This synthetic structural analogue of dopamine has a greater potency at β_2-adrenoceptors but less potency at dopaminergic receptors. It was thought to be devoid of α-adrenoceptor activity, but may, in fact, possess antagonist properties at this receptor (Martin and Broadley, 1995) and very weak agonism at β_1-adrenoceptors (Brown *et al.*, 1985; Bass *et al.*, 1987). Dopexamine's cardiovascular actions include chronotropy, inotropy and vasodilatation particularly in mesenteric, skeletal and renal beds (Mousdale *et al.*, 1988; Olsen *et al.*, 1993). These effects are believed to be due to a combination of direct β_2-adrenoceptor stimulation (vasodilatation and tachycardia), dopaminergic stimulation (decreasing renal and mesenteric vascular resistance) and an increased release of noradrenaline from sympathetic nerve terminals. However, these cardiovascular changes do not necessarily result in an increased myocardial oxygen demand (Dawson *et al.*, 1985).

Sympathomimetics

Phenylephrine. Phenylephrine is a selective α_1–adrenoceptor agonist predominantly causing proximal arterial effects (vasoconstriction) with terminal arteriolar sparing (Morelli *et al.*, 2008). Phenylephrine reduces pulmonary vessel calibre because of a combination of pulmonary vasoconstriction and also passively if a drop in cardiac output occurs (Aviado and Schmidt, 1957). A reflex bradycardia can often be seen with administration whether cardiac output is affected or not. Potent and selective α-adrenoceptor agonists decrease renal and splanchnic blood flow (Hoffbrand and Forsyth, 1973), which may give cause for concern when used to increase arterial pressure in critically ill patients.

Metaraminol. Metaraminol is a mixed direct- and indirect-acting sympathomimetic (Foster, 1966). It has direct action at α-adrenoceptors and increases the amount of noradrenaline in the synaptic cleft through displacement from pre-synaptic storage vesicles and by competing with noradrenaline for uptake-1, thus, leading to α-adrenoceptor and β_1-adrenoceptor agonism. A relatively long half-life is conferred by a resistance to MAO and COMT. Although this drug has β-adrenoceptor agonist actions, vasoconstriction causes a reflex bradycardia and may result in an overall fall in cardiac output (Dart, 2004). Pulmonary artery pressures can increase because of vasoconstriction although with variable changes in pulmonary flows due to the mixed effects on cardiac output (Aviado and Schmidt, 1957). It is mainly used during surgery or critical illness to reverse short-term episodes of hypotension.

Ephedrine. Ephedrine is a mixed direct- and indirect-acting sympathomimetic. It is taken up (U1) into nerve terminals and displaces noradrenaline from vesicles and nerve terminals to cause α-adrenoceptor effects. The problem of tachyphylaxis can occur with prolonged use of the drug because of depletion of noradrenaline (Moss and Renz, 2000). Ephedrine also exhibits mild direct β-adrenoceptor activity (Kobayashi *et al.*, 2003) with increases in cardiac output of up to 20% due to increases in heart rate and stroke volume (Cohn, 1965). Myocardial oxygen consumption is increased in common with all catecholamines and sympathomimetics. Other effects include bronchodilation, respiratory stimulation, mydriasis and tocolysis (Sasada and Smith, 2003). Studies in dogs suggest a decrease in pulmonary vascular resistance with an associated increase in pulmonary blood flow (Aviado and Schmidt, 1957). MAO and COMT resistance confers a longer half-life, and the drug is mainly excreted unchanged in the urine (Sasada, 2003).

PDEI

PDE has 11 isoforms, the important isoform for inotropic effects being PDE III. Methylxanthines (theophylline, caffeine) are non-selective PDEIs whereas amrinone, milrinone (bipyridines) and enoximone (imidazolone) are PDE III selective. These drugs enhance cAMP and PKA levels through non-receptor-dependent mechanisms and increase inotropy, chronotropy and lusitropy while decreasing preload and afterload (Figures 1 and 2). These agents are potent pulmonary vascular dilators and are considered particularly useful in the treatment of acute severe right heart failure and pulmonary hypertension (Greeley *et al.*, 2000).

Amrinone and milrinone. Amrinone and milrinone are bipyridine derivatives. Milrinone is more commonly used than amrinone because of the latter's tendency to cause dose-dependent thrombocytopaenia. This has been associated with the metabolite N-acetyl-amrinone (Lehtonen *et al.*, 2004). Milrinone is a more potent analogue of amrinone (Alousi and Johnson, 1986), which is mainly excreted unchanged in the urine. In common with all PDE III inhibitors, milrinone has a similar cardiovascular profile to dobutamine. However, milrinone increases heart rate to a lesser extent despite a greater tendency to decrease systemic vascular resistance. Milrinone decreases pulmonary vascular resistance and pulmonary artery pressure with a smaller effect on myocardial oxygen demand (Prielipp *et al.*, 1996; Petersen and Felker, 2008). This may be due to compensation by

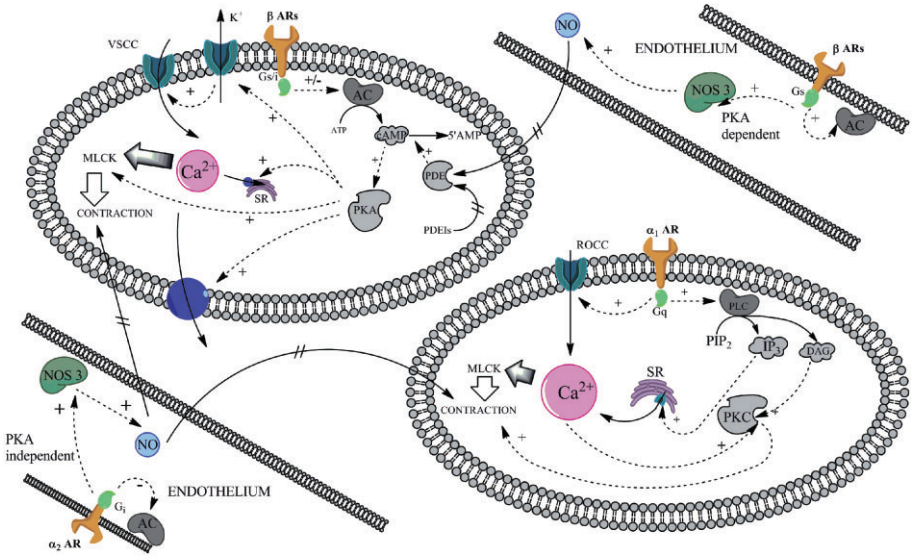

Figure 2

Intracellular mechanisms of catecholamine and PDEI modulation of vascular tone. Catecholamines and PDEIs modulate [Ca2+]i and, therefore, vascular smooth muscle cell tone as Ca2+ activates myosin light chain kinase (MLCK) and downstream contractile events. Vasoconstriction follows cAMP decreases or PLC stimulation. Vasodilatation follows cAMP increases. cAMP is broken down by PDE and generated by adenylate cyclase (AC). β adrenoceptors positively couple to AC by Gs whereas α2 adrenoceptors negatively couple via Gi. cAMP activates PKA, which is responsible for enhancing calcium pumping into sarcoplasmic reticulum (SR) and extracellular spaces, for MLCK inhibition and cellular hyperpolarization consequently inhibiting voltage-sensitive calcium channel (VSCC). α1 adrenoceptors positively couple to PLC via Gq resulting in the generation of inositol 1,4,5 trisphosphate (IP3) and DAG from phosphatidylinositol 4,5 bisphosphate (PIP2). IP3 activates SR calcium channels, increasing [Ca2+]i while DAG and calcium both stimulate PKC. PKC enhances contractile element sensitivity. Receptor-operated calcium channels (ROCC) are positively coupled to α1 adrenoceptors via non Gq subunits. NO is generated by NOS 3 in endothelium following α2 and β adrenoceptor ligation. NO diffuses to vascular smooth muscle resulting in protein kinase G mediated decreases in calcium, PDE inhibition and vasodilatation. The endothelium is thus a powerful modulator of vascular tone.
5′AMP, 5′ adenosine monophosphate; Gs/i/q, relevant G-protein α subunit.

preload and afterload reductions, leading to decreased ventricular wall stress (Colucci, 1991). Left ventricular pressure–volume loops suggest that lusitropy is enhanced and right ventricular afterload is decreased (Colucci, 1991). There has been some suggestion that milrinone does not, in fact, increase contractility to any significant degree, the vasodilator actions being more significant, although this is controversial (Ludmer *et al.*, 1986; Royse *et al.*, 2007).

Enoximone. Enoximone is an imidazolone and a selective PDE III inhibitor. *In vivo* comparisons demonstrate less inotropy and chronotropy, but more lusitropy when compared with milrinone. However, at clinical doses, only milrinone produced significant inotropic and lusitropic effects (Zausig *et al.*, 2006). Enoximone may increase fat metabolism in comparison with glucose, which could be beneficial in septic shock (Trager *et al.*, 2001). Enoximone is metabolized by saturable enzyme systems and the active metabolites are renally excreted, although the parent compound itself is not (Lehtonen *et al.*, 2004). The half-lives of PDE III inhibitors increase in renal failure, which is common among critically ill patients.

Aminophylline. Aminophylline is the ethylenidiamine salt of theophylline and was commonly used in the treatment of severe acute bronchial asthma and also as a treatment for increasing urine output in impending acute kidney injury. Aminophylline also has mild inotropic activity and continues to be used, albeit infrequently, for this purpose.

Levosimendan

Levosimendan is a myofilament calcium sensitizer and a novel inotrope that increases contractility without increasing cAMP levels appreciably at clinically recommended doses. Unlike other inotropes, levosimendan does not exert its action through potentially harmful increases in intracellular Ca^{2+}. This may explain why this agent does not impair diastolic relaxation and cardiac rhythm, and has less harmful effects on myocardial energetics (Toller and Stranz, 2006; Tavares *et al.*, 2008). Levosimendan binds to the N-terminal of troponin C with high affinity, but at $[Ca^{2+}]_{i,}$, which are only reached in systole, prolonging the interaction of myosin and actin filaments through inhibition of troponin I. This contrasts with other filament sensitizers that remain bound at Ca^{2+} concentrations, which occur in diastole, thus, impairing diastolic relaxation and ventricular compliance (Toller and Stranz, 2006; Tavares *et al.*, 2008). Levosimendan has PDE III inhibitory actions, but these are not thought to be clinically significant (Toller and Stranz, 2006). Importantly, the levosimendan metabolite OR-1896 has similar calcium-sensitizing actions to the parent molecule, maintaining the inotropic effect of levosimendan once an infusion is stopped (Toller and Stranz, 2006). The cardiovascular effects of levosimendan include

increased heart rate when high-dose loading and infusions are used, possibly via baroreceptor-mediated pathways. In vascular tissue, levosimendan acts as a vasodilator by decreasing the sensitivity of myofilaments to Ca^{2+} and activating of K^+ channels. This results in hyperpolarization, decreased Ca^{2+} entry and vasodilatation (Toller and Stranz, 2006; Petersen and Felker, 2008). Levosimendan is generally used for 24 h due to OR-1896 accumulation, which has a terminal half-life of 96 h (Toller and Stranz, 2006).

Changes to pharmacokinetics and pharmacodynamics of inotropic agents during critical Illness

Alterations in receptor and intracellular signalling pathways. Agonist binding to adrenoceptors causes coupling with G proteins (Figures 1 and 2). These G proteins consist of three subunits (α, β and γ), the type of α subunit denoting the type of G-protein (G_s is $G_{\alpha(s)\beta\gamma}$). On coupling, α subunits exchange GDP for GTP, dissociate from the complex and are active until the GTP is hydrolysed back to GDP. α-GDP then reassociates with the βγ subunit complex and is available to couple with another adrenoceptor. The duration of signalling is inversely related to the speed with which α-GTP is hydrolysed to α-GDP, a process promoted by regulator of G-protein signalling (RGS) molecules (Hendriks-Balk *et al.*, 2008). RGS mRNA is increased by endotoxin and may, therefore, constitute one mechanism of diminished adrenoceptor agonist responses in sepsis (Panetta *et al.*, 1999; Hendriks-Balk *et al.*, 2009; Riekenberg *et al.*, 2009). β-adrenoceptors couple predominantly to G-stimulatory (G_s) proteins but also couple to G-inhibitory (G_i) proteins (Bohm *et al.*, 1995; Martin *et al.*, 2004). Prolonged β_2 adrenoceptor agonism induces both reductions in G_s and increases in G_i. This switch to G_i signalling has been confirmed in human and animal sepsis studies (Bohm *et al.*, 1995; Bernardin *et al.*, 1998; Wu *et al.*, 1999; 2003). Evidence also exists of a predominant down-regulation of most adenylate cyclase isoforms in several tissues in response to endotoxaemia, potentially further affecting adrenoceptor signalling processes (Risoe *et al.*, 2007).

Sustained adrenoceptor agonism frequently occurs in sepsis and may result in desensitization and down-regulation of α and β adrenoceptors (Heck and Bylund, 1997). This occurs partly through the above mechanisms and also by activation of PKA and PKC, which phosphorylate GPCRs indiscriminately. Agonist-bound adrenoceptors are also specifically phosphorylated by G-protein receptor kinases (GRKs). Both mechanisms result in receptor internalization, although GRK phosphorylation of activated receptors also results in further uncoupling from G_α signalling subunits through the attachment of β-arrestin molecules. GRK 2 (phosphorylates β_2 adrenoceptors) may be up-regulated in sepsis (Kadoi *et al.*, 2002). In addition to these effects on existing adrenoceptors and their signalling partners, sustained adrenoceptor agonism also reduces generation of new adrenoceptors. As a result, adrenoceptors become refractory to agonism, signal for shorter periods and in atypical ways. These changes occur in heart failure but are more pronounced in the heart in sepsis because of synergistic effects of endotoxin and TNF-α. Sepsis also up-regulates other related pathways such as PDE III (Choi *et al.*, 2009).

Free radicals and the auto-oxidation of catecholamines. Sepsis is associated with the generation of NO and subsequently peroxynitrite, which deactivates catecholamines (Takakura *et al.*, 2003) and disturbs adrenoceptor function (Takakura *et al.*, 2002; Lewis *et al.*, 2005). Catecholamines are also degraded by superoxide to quinones. This is autocatalytic as superoxide is regenerated. This reaction may be more important in shock states when pH decreases and free radical and catecholamine levels are elevated. Quinones are neurotoxic (Smythies and Galzigna, 1998) and cardiotoxic (Yates *et al.*, 1981; Bindoli *et al.*, 1992; Neri *et al.*, 2007). The inverse relationship between plasma levels of adrenochromes and catecholamines suggests refractoriness to catecholamine therapy in shock states may relate to this deactivation (Macarthur *et al.*, 2000), in particular by polymorphonuclear leucocytes (Matthews *et al.*, 1985).

Additional effects of inotropes and vasopressors in critical illness

Regional blood flow. Reductions in renal and hepatosplanchnic blood flow are a concern in critical illness. However, there is no evidence that this occurs in resuscitated states of pathological vasodilatation treated with noradrenaline (Reinelt *et al.*, 1997), and there may be some improvement in microvascular flow and tissue oxygenation (Albanese *et al.*, 2004; Jhanji *et al.*, 2009b). Dopamine, noradrenaline and adrenaline produce similar splanchnic blood flow in moderate septic shock, although in severe septic shock, adrenaline decreases splanchnic blood flow when compared with noradrenaline (De Backer *et al.*, 2003). Phenylephrine also reduces splanchnic blood flow when compared with noradrenaline in septic shock (Reinelt *et al.*, 1999). Although dopexamine may improve tissue oxygenation and microvascular flow (Jhanji *et al.*, 2010), the evidence for this in the hepatosplanchnic bed is equivocal and may only occur in some patient groups (Renton and Snowden, 2005). Vasopressin analogues also decrease hepatosplanchnic blood flow, but have unique effects on intrarenal haemodynamics in shock (Albert *et al.*, 2004).

Metabolic changes. α adrenoceptors inhibit the pancreatic release of insulin whereas β adrenoceptors stimulate glucagon release, and hepatic glycogenolysis and gluconeogenesis. This increases serum glucose concentration. Catecholamines also stimulate lipolysis, increasing plasma free fatty acids. These effects are particularly pronounced with adrenaline (Ensinger *et al.*, 1995) and relate to the intrinsic ability of the catecholamines to generate cAMP (Barth *et al.*, 2007). The effect on protein catabolism is complex as β_2 agonism can inhibit proteolysis (Navegantes *et al.*, 2001) but hypermetabolic states with protein breakdown result when catecholamine levels remain elevated. Dopamine suppresses growth hormone and thyroid-stimulating hormone release, potentially exacerbating protein losses (Schilling *et al.*, 2004). β_2 adrenoceptor-mediated increases in lactate relate to increased Na^+/K^+ ATPase activity, increasing VO_2 (Levy *et al.*, 2008). VO_2 also increases through β adrenoceptor-mediated increases in substrate flux and mitochondrial uncoupling. Unlike in health (Bearn *et al.*, 1951), in the hepatosplanchnic bed in sepsis, splanchnic VO_2 may not necessarily relate directly to hepatic metabolic workload though (Reinelt *et al.*, 1997; 1999). Although catecholamines directly cause mitochondrial

complex inhibition, mitochondrial respiratory efficiency during endotoxaemia may improve in some tissues (Porta *et al.*, 2006; 2009; Regueira *et al.*, 2008). Studies suggest that adrenaline, noradrenaline and dobutamine may be better in this regard than dopamine (Jakob *et al.*, 2002; De Backer *et al.*, 2003; Guerin *et al.*, 2005). Mitochondrial uncoupling protein (UCP) 2 expression is up-regulated in the heart in sepsis (Roshon *et al.*, 2003), possibly as a means to decrease free radical production (Boss *et al.*, 2000). However, this decreases mitochondrial Ca^{2+} uptake and permits a greater degree of arrhythmogenic Ca^{2+} sparking in addition to impairing excitation–contraction efficiency (Turner *et al.*, 2011). It is important to note that arrhythmias occur more frequently in association with dopamine treatment for septic shock (De Backer *et al.*, 2010) and that quinone-induced mitochondrial UCP and transition pore opening may be a mechanism of cytotoxicity (Berman and Hastings, 1999).

Bacterial growth. Iron is required for several intracellular processes essential for the growth of bacteria. Some strains of bacteria sequester iron by secreting siderophores that bind iron and reuptaking the siderophore–iron complexes. Catecholamines, particularly noradrenaline, can increase bacterial iron uptake, stimulating growth (Coulanges *et al.*, 1997). There is also some evidence that catecholamines act as host signals to enhance virulence factors and gene transfer in commensal organisms such as *Escheria coli* (Hughes and Sperandio, 2008; Peterson *et al.*, 2011).

Immune system. Adrenoceptors can be identified in all immune cells as well as in the endothelium and play a central role in many aspects of the immune response, which is clearly of particular importance during critical illness. Acutely, adrenaline infusion results in a β-adrenoceptor-mediated leucocytosis, predominantly cytotoxic cells, from the marginating pool (Rogausch *et al.*, 1999; Dimitrov *et al.*, 2010). However, the initial leucocytosis seen in endotoxaemia is α_1 adrenoceptor mediated (Altenburg *et al.*, 1997). Various catecholamines have been shown to either increase (Horn *et al.*, 2005) or decrease neutrophil–endothelial (Boxer *et al.*, 1980; Schmidt *et al.*, 1998) and lymphocyte–endothelial interactions (Carlson *et al.*, 1996). Different catecholamines modulate the expression of integrins on the surface of leucocytes (Trabold *et al.*, 2007), decrease chemotaxis (Silvestri *et al.*, 1999) and phagocytosis (Gosain *et al.*, 2007), decrease neutrophil α-defensin secretion (Riepl *et al.*, 2010), and decrease respiratory burst in neutrophils (Weiss *et al.*, 1996; Lunemann *et al.*, 2001). There are also effects on lymphocyte proliferation and differentiation such that $CD8^+$ cells are decreased and antibody secretion by B-cells is decreased (Bergquist *et al.*, 1994; Qiu *et al.*, 2005). α_1 and β_2 adrenoceptor mechanisms increase apoptosis in lymphocytes (Jiang *et al.*, 2009), although dopamine-induced prolactin suppression may also play a role (Zhu *et al.*, 1997). Catecholamines have complex effects on cytokine release, partly dependent on the stage of sepsis (Bergmann *et al.*, 1999). In general, pro-inflammatory cytokine release is reduced by β_2 adrenoceptor agonism, while anti-inflammtory cytokines such as IL-10 increase (Szabo *et al.*, 1997; Muthu *et al.*, 2005). α-adrenoceptor agonism results in opposite effects. α_2 adrenoceptors control neutrophil homing in endotoxaemia (Abraham *et al.*, 1999), and G_i signalling is important in leucocyte extravasation (Pero *et al.*, 2007), but the situation may differ in haemorrhage (Arcaroli *et al.*, 2002). In general, dopamine and adrenaline appear to have immunosuppressive actions while noradrenaline is less so, probably because of a weaker effect at β_2 adrenoceptors. Endogenous and exogenous catecholamines may contribute to late-phase immunosuppression commonly seen after major surgery, trauma or sepsis. Alternative agents such as vasopressin also have immune effects (Hofstetter *et al.*, 2007; Russell and Walley, 2010).

Apoptosis, inflammation and other receptor systems. Other than apoptosis in lymphocytes (Jiang *et al.*, 2009), several catecholamines and PDEIs induce heart, vascular smooth muscle and skeletal muscle myocyte apoptosis (Burniston *et al.*, 2005; Garcia-Cazarin *et al.*, 2008). Quinone molecules have been shown to open the mitochondrial permeability transition pore (Berman and Hastings, 1999), an important step in inducing cell death pathways. Inflammatory pathways under catecholamine modulation are those centred on NF-κB activation; these are responsible for cytokine gene regulation (Arcaroli *et al.*, 2002). Enzymes involved in cell survival, such as glycogen synthase kinase 3B (Ballou *et al.*, 2001), PI-3-kinase (Yamboliev and Mutafova-Yambolieva, 2005) and ERK (Wright *et al.*, 2008) have also been shown to be activated by α_1 and α_2 agonism, often through actions of $G_{\beta\gamma}$ subunits. Proteosomal inhibition and concomitant up-regulation of heat shock proteins have also been demonstrated (Costa *et al.*, 2009). Although this is deemed beneficial in ischaemia reperfusion, persistent adrenergic agonism is likely to increase apoptotic and anti-inflammatory responses. This may contribute to the cardiac dysfunction (Moretti *et al.*, 2002; Chopra and Sharma, 2009), immune anergy and organ dysfunction seen with sepsis. Transactivation of endothelial growth factor receptor (EGFR) by α adrenoceptor agonism has been shown to be important in vascular contractile responses (Hao *et al.*, 2006), but the significance of this signalling in the context of critical illness is not known.

Coagulation & platelets. Both α and β adrenoceptors mediate the exocytosis of von Willebrand factor (vWF), clotting factor VIII, tissue plasminogen activator and chemoattractant IL-8 from Weibel–Palade bodies in endothelial cells. However, PKA results in partial stabilization of these bodies while G_q signalling does not (Rondaij *et al.*, 2006). The activation of G_i by platelet α_2 adrenoceptors is necessary to decrease a tonic inhibition on platelet aggregation (Maayani *et al.*, 2001). The aggregation of platelets is enhanced only in the presence of very high levels of circulating catecholamines (Ikarugi *et al.*, 2003) such as in sepsis, as β-adrenoceptor stimulation probably mitigates that of α stimulation at lower plasma catecholamine levels (Yu and Latour, 1977). Platelet activation may impede microvascular flow and tissue oxygen delivery by a combination of enhanced platelet–leucocyte–endothelial interactions (von Hundelshausen *et al.*, 2009) and microthrombus formation. Although epinephrine can increase factor VIII and platelet aggregation, the severity of sepsis is actually associated with diminished platelet aggregation (Yaguchi *et al.*, 2004), and epinephrine has been shown to decrease coagulation in endotoxaemia (van der Poll *et al.*, 1997).

Gastrointestinal tract. The gut is richly innervated and is, therefore, responsive to neuronally released and circulating catecholamines (De Ponti *et al.*, 1996). In critical illness the use of catecholamines and degree of motility disturbance are associated (van der Spoel *et al.*, 2006), although the severity of illness and use of sedative drugs disturbs motility and also associates with catecholamine use. Endogenous catecholamines have all been shown to directly inhibit motility in the colon, ileum and upper gastrointestinal tract *in vitro* (Beani *et al.*, 1969; Kosterlitz *et al.*, 1970) and *in vivo* (Dive *et al.*, 2000). *In vitro* studies suggest this may be less of an issue with some synthetic catecholamines (Fruhwald *et al.*, 2000).

Clinical trials of inotropes and vasopressor agents

Sepsis. Septic shock is a common presentation in the critical care unit, resulting in impaired ventricular function, pathological vasodilatation, hypovolaemia, deranged microvascular flow and increased capillary permeability (Dellinger, 2003). Inotropic and vasopressor agents are, therefore, among the most important therapies in the treatment of this syndrome. However, despite the fundamental importance of appropriate vasoactive drug use in the treatment of patients with septic shock, the clinical evidence base is surprisingly limited. In combination with i.v. fluids, the objective of vasoactive drug therapy is to restore cardiac output, arterial pressure, and hence, tissue perfusion and oxygenation. Once adequately fluid-resuscitated a combination of vasopressor and/or inotropic agents may be used to achieve the desired physiological targets. There is an extensive debate regarding the most appropriate physiological goals for vasoactive drug therapy in septic shock, as well as in other patient groups. It is beyond the scope of this review to explore this issue in detail. However the most important goals that continue to be debated are mean arterial pressure, cardiac output, systemic oxygen delivery (DO_2) and, more recently, mixed/central venous saturation ($ScvO_2$). However, there is also a growing body of evidence that vasoactive drug therapies exert many important effects within the microcirculation, which may not be immediately identified from changes in global haemodynamics (De Backer *et al.*, 2006; Jhanji *et al.*, 2009a; 2010). There is no standard dosing regimen for inotropic agents; there is considerable variability in practice. Further research into dose selection is likely to prove of even greater value than research comparing different agents. However, it seems likely that the optimal approach will involve the use of inotropic agents in the lowest effective dose and for the minimum period of time. There has been some confusion between the effects of treatments used to achieve haemodynamic goals and the monitoring device used to provide the data. In particular there has been some concern regarding excess mortality related to use of the pulmonary artery catheter. However, three large multi-centre trials have now confirmed the safety of this device (Richard *et al.*, 2003; Sandham *et al.*, 2003; Harvey *et al.*, 2006).

The majority of vasoactive agents in current use are catecholamine based. Adrenaline, noradrenaline and dobutamine are probably the most commonly used agents. A number of clinical trials have explored the use of specific haemodynamic goals such as cardiac index, DO_2 and $ScvO_2$ (Hayes *et al.*, 1994; Gattinoni *et al.*, 1995; Rivers *et al.*, 2001). The use of such goals may be effective in the early stages of resuscitation of patients with septic shock (Rivers *et al.*, 2001). However, later application for prolonged periods or the aggressive pursuit of goals in patients who do not respond has proved ineffective (Gattinoni *et al.*, 1995; Alia *et al.*, 1999) and may even be harmful (Hayes *et al.*, 1994). Use of high-dose catecholamine therapy to achieve purely physiological therapeutic goals may contribute to excess mortality (Rona, 1985). In recent years, the use of adrenaline has declined in favour of dobutamine because the potential vasodilator effects of the latter agent are thought to improve tissue microvascular flow. However, in a multi-centre trial, the use of a combined regimen of dobutamine and noradrenaline was associated with similar clinical outcomes to adrenaline alone (Annane *et al.*, 2007). In another trial, adrenaline was compared directly with noradrenaline, again with similar mortality rates (Myburgh *et al.*, 2008). Interestingly more patients in the adrenaline group were withdrawn primarily because of transient metabolic effects of this drug (Myburgh *et al.*, 2008). PDEIs are also an option in the treatment of septic shock. Like dobutamine, the vasodilator properties of this group of agents are believed to enhance tissue microvascular flow, although this has not been clearly demonstrated in studies in human sepsis. However, the consequent reduction in arterial pressure may necessitate an increased dose of vasopressor agent and the longer half-life, which is further increased in renal failure (Lehtonen *et al.*, 2004), can limit the flexibility of this treatment approach.

In terms of vasopressor therapy, the findings of a recent large multi-centre trial comparing dopamine with noradrenaline in a mixed population of critically ill patients suggest noradrenaline use is associated with better clinical outcomes (De Backer *et al.*, 2010). It is likely that these findings, in fact, relate to harmful chronotropic effects of dopamine resulting in tachycardia and perhaps myocardial ischaemia (De Backer *et al.*, 2010). The role of dopamine in the prevention and treatment of acute kidney injury is discussed below. There is continued interest in the use of vasopressin in septic shock as this agent may have a particular role in the treatment of catecholamine-resistant loss of vascular tone. Both terlipressin and aVP have been used in this context, although the latter has been more thoroughly studied in humans. Findings of a large trial suggested no difference in clinical outcomes between noradrenaline and a combined regimen of aVP and noradrenaline (Russell *et al.*, 2008). However, there is some concern that the pure vasoconstrictor actions of vasopressin may result in further impairment of microvascular flow, particularly in the hepatosplanchnic bed (Martikainen *et al.*, 2003; Westphal *et al.*, 2004). Vasopressin is likely to be of value in the case of hypotension due to vasodilatation but may not necessarily be beneficial where this is due to low cardiac output as the combination of coronary vasoconstriction and increased ventricular afterload may result in further compromise of myocardial function (Muller *et al.*, 2008; Simon *et al.*, 2009). Furthermore, vasopressin analogues (particularly terlipressin), have a longer half-life than the catecholamines and cannot be titrated to effect as easily. Further research directly comparing the effects of vasopressin and noradrenaline may provide more useful guidance on the use of these agents (Russell *et al.*, 2008; Gordon *et al.*, 2010).

In one very small randomized trial, there were no differences in physiological parameters in patients treated with phenylephrine compared with noradrenaline in septic shock (Morelli *et al.*, 2008). However it is questionable whether the effects of pure α_1-agonism are always beneficial in septic shock, again due to concerns regarding the effect of pure vasoconstrictor agents on microvascular flow. There is some limited data to suggest that metaraminol could be used as a vasopressor agent in septic shock (Natalini *et al.*, 2005). Because this agent may be administered via a peripheral vein as well as a central venous catheter, it has some application as a vasopressor in the early period of stabilization when a patient with haemodynamic shock is first identified but has yet to have a central venous catheter inserted.

There may be important interactions between inotropic drugs and patient genotype (Nakada *et al.*, 2010). The CysGlyGln haplotype of the β_2 adrenoceptor gene is associated with altered responses to adrenergic agonists in asthmatic patients. Recent research has suggested that certain polymorphisms of this adrenoceptor gene may be associated with greater inotrope requirements and increased mortality from septic shock. Further understanding of the pharmacogenomics of inotropic agents may allow more appropriate drug therapy for individual patients. However, there is very little research data in this area at present.

Acute kidney injury. There has been some interest in the use of inotropic agents, particularly dopaminergic agents, in the prophylaxis and treatment of acute kidney injury. For many years, the renovascular effects of low-dose dopamine were believed to be beneficial in both respects. Certainly in the 0–5 $\mu g \cdot kg \cdot min^{-1}$ dose range, dopamine promotes diuresis and natriuresis, but there has been little evidence that this effect ameliorates any harmful effects on global renal function. The findings of a randomized trial confirm that the physiological effects of this agent in terms of renal function are not associated with any improvement in the need for haemodialysis or other relevant clinical outcomes (Bellomo *et al.*, 2000). Since the publication of these findings, most critical care physicians have stopped using dopamine for this indication (Kellum and Decker, 2001). Although not an inotrope but, in fact, an antihypertensive agent, the selective D_1 agonist and dopamine analogue fenoldopam has also been studied for the prevention of acute renal failure in various settings. While still requiring a definitive trial to prove the case, there is current evidence suggesting fenoldopam may ameliorate acute kidney injury, although not from contrast-induced causes (Halpenny *et al.*, 2002; Stone *et al.*, 2003; Bove *et al.*, 2005; Morelli *et al.*, 2005; Tumlin *et al.*, 2005; Landoni *et al.*, 2007; 2008). Contrast-induced nephropathy occurs in 11% of critically ill patients and is defined as an absolute ($0.5\ mg \cdot dL^{-1}$) or relative increase (>25%) in serum creatinine over 48–72 h following the use of nephrotoxic radio-opaque contrast agents in diagnostic imaging procedures (Mehran and Nikolsky, 2006; Rashid *et al.*, 2009). There has also been some interest in the effect of dopexamine on perioperative acute kidney injury. However, these small studies have not clearly confirmed or refuted such an effect of dopexamine infusion (Schmoelz *et al.*, 2006; Jhanji *et al.*, 2010).

Severe heart failure and cardiogenic shock. Of all categories of patients who require inotropic therapy, those with severe heart failure are the most challenging to treat. In most cases, inotropes can only be regarded as a bridging therapy to stabilize patients while definitive, often surgical, interventions can be arranged. Few agents have been associated with improved outcomes in clinical trials and several with reduced survival. This creates a dilemma for the clinician faced with a patient with severe haemodynamic shock who is unlikely to survive without some form of restoration of homeostasis through improved cardiac output and arterial pressure. It would not be considered ethical to randomize such patients into the placebo arm of a clinical trial that does not provide some form of vasoactive drug therapy. Thus, it seems likely that vasopressor and inotropic therapies do prolong survival, however, briefly.

Findings of a recent large multi-centre trial discussed above suggest that vasopressor therapy with dopamine may be associated with an increased mortality when compared with noradrenaline. This effect was most obvious in the subgroup of patients with heart failure in whom the significant chronotropic effects of dopamine are most likely to cause harm due to myocardial ischaemia (De Backer *et al.*, 2010). It seems likely that the use of dopamine will decline following this trial. Unfortunately, the findings of other trials have provided little in the way of clear guidance for clinical practice.

Neither dobutamine nor milrinone has proved to be superior to the other in the treatment of heart failure (Petersen and Felker, 2008). Furthermore milrinone treatment is associated with an increased mortality over baseline in heart failure patients (Packer *et al.*, 1991). Reasons for this are unclear, but PDE III inhibition causes increased plasma renin levels through non-renal baroreceptor-, cAMP-mediated mechanisms in juxtaglomerular cells (Chiu and Reid, 1996; Chiu *et al.*, 1999).

There has been great interest in the use of the novel agent levosimendan in patients with severe heart failure and cardiogenic shock. Early data have suggested that treatment with levosimendan in these circumstances may improve cardiac performance with little or no increase in myocardial work. Initial small clinical trials supported this theory with evidence of improved haemodynamics and, perhaps, survival after a 24 h infusion. However, larger trials failed to confirm this survival benefit when compared with dobutamine therapy in patients with heart failure (Mebazaa *et al.*, 2007). When compared with placebo, levosimendan use was associated with increased mortality at 90 days, and a higher incidence of hypotension and arrhythmia (Petersen and Felker, 2008). However, given the problematic evidence base for inotropic therapy in heart failure, there is still an argument for the use of levosimendan, in particular, after cardiac surgery (Braun *et al.*, 2006) and in patients with right heart failure where pulmonary vasodilator effects may be important.

Major surgery. Anaesthetists commonly use various mild inotropic or vasopressor agents in bolus doses to correct the cardiovascular effects of general and regional anaesthesia. Ephedrine, phenylephrine and metaraminol have proved popular for this indication. A small proportion of patients who undergo major surgery will develop haemodynamic shock and require an inotrope or vasopressor infusion. Such cases are generally managed in a similar way to that described for

patients with septic shock. However, there has also been a long-standing interest in the use of inotropic agents as part of a 'goal-directed' approach to haemodynamic therapy with pre-determined goals, including cardiac index, systemic oxygen delivery and/or venous saturation. In fact, most clinical trials of inotropic agents in patients undergoing major surgery have related to this approach, which may improve outcome by augmenting oxygen delivery to the tissues (Jhanji *et al.*, 2010). Once again, although a number of clinical trials of goal-directed perioperative haemodynamic therapy have been performed, most have been small single-centre trials. The findings of these trials have proved inconsistent because of important methodological variations including differences in patient group, timing and duration of interventions, treatment end-points, therapies used to achieve end points, and choice of monitoring technology. Some trials identified reductions in morbidity (Berlauk *et al.*, 1991; Polonen *et al.*, 2000; Pearse *et al.*, 2005) and mortality (Boyd *et al.*, 1993; Wilson *et al.*, 1999; Lobo *et al.*, 2000). Others, however, failed to show any benefit (Ueno *et al.*, 1998) particularly in the case of vascular surgery (Bender *et al.*, 1997; Ziegler *et al.*, 1997; Valentine *et al.*, 1998; Bonazzi *et al.*, 2002).

Dopexamine has been the most frequently investigated agent in the surgical population. This agent may have specific beneficial effects on tissue microvascular flow and oxygenation in patients following major gastrointestinal surgery (Jhanji *et al.*, 2010). Interestingly, the findings of a metaregression analysis suggest that dopexamine may, in fact, have a biphasic effect on outcome, with improved survival in low doses (<1 $\mu g \cdot kg \cdot min^{-1}$) but reduced survival at higher doses (Pearse *et al.*, 2008). The β_2-agonist effects of dopexamine often result in significant tachycardia at higher doses, and, in common with dopamine, it seems likely that this may be associated with an increased incidence of myocardial ischaemia. Once again, these data indicate the importance of using inotropes at the minimum effective dose.

Cardiac arrest

Findings from animal studies had long suggested a role for adrenaline in resuscitation prior to the discovery of modern cardiopulmonary resuscitation (CPR) techniques for cardiac arrest (Crile and Dolley, 1906). Later studies suggest vasoconstrictor effects of adrenaline may be more important than inotropy in this setting (Paradis *et al.*, 1990; Pearson and Redding, 1963a,b; Yakaitis *et al.*, 1979). In clinical studies, i.v. drug administration following out-of-hospital cardiac arrest was associated with increased short-term survival but not in survival to hospital discharge or improved neurological outcomes. Similarly, comparisons of selective α-adrenergic agonists, vasopressin, high doses of adrenaline/noradrenaline with standard-dose adrenaline do not suggest any differences in survival or neurological outcomes in cardiac arrest (Callaham *et al.*, 1992; Patrick *et al.*, 1995; Woodhouse *et al.*, 1995; Gueugniaud *et al.*, 1998; 2008; Stiell *et al.*, 2001; Perondi *et al.*, 2004; Wenzel *et al.*, 2004; Callaway *et al.*, 2006). Inconsistencies between animal and clinical studies may reflect the validity of laboratory models (Reynolds *et al.*, 2007). Considerable uncertainty remains over the role of vasoactive therapy in cardiac arrest. Current guidelines place greater importance on effective chest compressions, early defibrillation and post-resuscitation care. (Hazinski *et al.*, 2010; Nolan *et al.*, 2010). However, use of adrenaline, particularly in cases of anaphylaxis, is still recommended in the absence of a superior alternative.

Conclusions

Despite widespread use, the evidence base for the use of inotropes and vasopressors in critically ill patients is limited. Clearly, many patients would not survive without inotropic support, but there is, nonetheless, considerable variation in clinical practice. Few large randomized controlled trials directly compare agents in terms of survival or other patient relevant outcomes, which is the level of evidence increasingly demanded by clinicians. However, current practice can be improved through a more detailed understanding of the diverse actions of these agents and the potential toxic effects. It would seem prudent to use minimum necessary doses of such agents until the evidence base improves.

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Conflict of interest

RP is a named inventor on a lapsed patent application relating to a specific use for dopexamine.

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