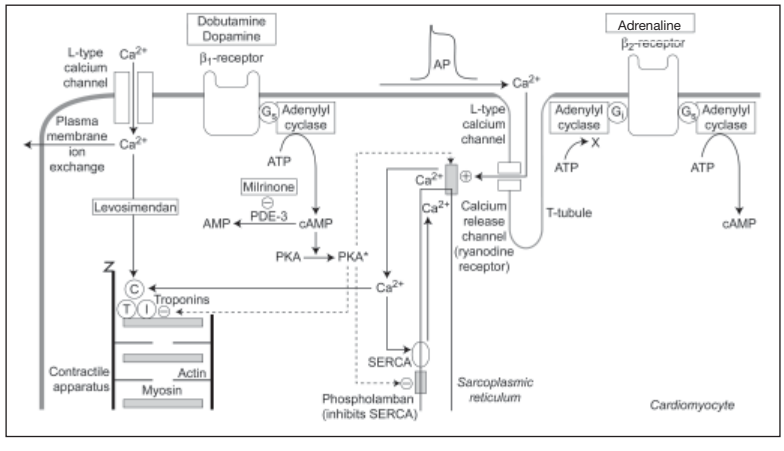
Intravenous inotropic agents in heart failure

Inotropes are some of the most commonly used drugs in intensive care. However, their value in treating patients with heart failure is limited and prolonged use is associated with an increased mortality. Nevertheless inotropic agents increase cardiac contractility and can improve the cardiac output of patients with heart failure.

The action of commonly used inotropic agents is best understood by considering the signalling pathways that regulate normal myocyte contraction and peripheral vascular tone (Braunwald, 2005; Opie, 2005). Calcium cycling within the cardiac myocyte generates the signal which initiates and terminates the interaction between actin and myosin that generates myocyte contraction (*Figure 1*) (Bers, 2000). The amplitude of the calcium signal is regulated by the β-adrenoceptor/cyclic AMP (cAMP) pathway. β-adrenergic stimulation, whether by noradrenaline (norepinephrine) released from sympathetic nerves or by exogenously administered inotropic drugs, leads to increased myocardial contractility (Bristow et al, 2005). β-adrenergic receptors are coupled to adenylyl cyclase by the stimulatory G protein G_s. Adenylyl cyclase catalyses the conversion of ATP to cAMP, a ubiquitous second messenger that, in the cardiomyocyte, is positively inotropic and chronotropic.

Figure 1. Simplified schema of the regulation of cardiomyocyte contraction. AMP = adenosine monophosphate; AP = action potential; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; G_i = inhibitory G coupling protein; G_s = stimulatory G coupling protein; PDE-3 =phosphodiesterase type-III; PKA = c-AMP-dependent protein kinase A; PKA* = activated PKA; SERCA = sarcoendoplasmic reticulum calcium ATPase.



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The β2 receptor similarly couples with G_s but also with an inhibitory protein G_i. The failing human heart is already adrenergically activated which increases cardiac contractility, heart rate and cardiac output at least in the short term (Rundqvist et al, 1997) but the response to β-adrenergic stimulation is decreased as a result of β1 receptor down-regulation (Bristow, 1993).

Increased levels of cAMP activate cAMP-dependent protein kinase A. Protein kinase A then phosphorylates a number of proteins including the L-type calcium channel and the ryanodine receptor so increasing calcium release into the cytosol; phosphorylation of phospholamban removes its inhibition of the sarcoendoplasmic reticulum calcium ATPase increasing calcium reuptake into the sarcoplasmic reticulum during diastole (Koss and Kranias, 1996). The action of cAMP is terminated by its breakdown to AMP by phosphodiesterase type III (Movsesian et al, 1991).

Clinically available intravenous inotropes act by stimulating β-receptors (dobutamine, adrenaline (epinephrine), noradrenaline, isoprenaline (isoproterenol) and dopamine), inhibition of the breakdown of cAMP (milrinone and enoximone) or by the increased sensitivity of the contractile process to intracellular calcium (levosimendan) (Sonnenblick et al, 1979; Edes et al, 1995; Rocco and Fang, 2006).

Many of these agents also alter peripheral vascular tone. Contraction of the vascular smooth muscle cell is subject to regulation by several intracellular signalling pathways (*Figure 2*). Vasoconstriction is primarily mediated by the α-1 adrenoceptor pathway while dilatation is regulated by both the cAMP- and cyclic GMP-dependent pathways (Hoffman, 2004; Katzung and Chatterjee, 2004). Agonist binding to the β2 receptor leads to stimulation of adenylyl cyclase and an increase in cAMP which acts by accelerating the inactivation of myosin light chain kinase, so preventing the phosphorylation of myosin light chains and inhibiting smooth muscle contraction. In tissues where dopaminergic receptors are present, dopamine induces vasodilatation by the cAMP pathway. Once again, the action of cAMP is terminated with breakdown by phosphodiesterase type III.

Inotropes that alter vascular tone change ventricular loading conditions as well as altering the relationship between blood pressure and cardiac output.

Sympathomimetic drugs may cause vasoconstriction via the α-1 receptor (e.g. noradrenaline, adrenaline) or vasodilatation via the dopaminergic or β2 receptors (e.g. dopamine, dobutamine, isoprenaline and adrenaline). Milrinone and enoximone will produce vasodilatation by inhibiting phosphodiesterase type III. Levosimendan opens ATP-dependent potassium channels as well as inhibiting phosphodiesterase type III which both result in vasodilatation. While the signalling pathways in vascular smooth muscle are universal, the response in different tissues will depend on the level of expression of the various receptors in each tissue. Similar mechanisms exist in the systemic and pulmonary circulations.

Specific agents

The endogenous catecholamines adrenaline and noradrenaline have short half lives as a result of neuronal reuptake and degradation by catechol O-methyltransferase in the liver and lung. Synthetic derivatives such as dobutamine and isoprenaline have similar properties but different affinities for adrenergic receptors. This group of drugs is administered by continuous intravenous infusion and steady state plasma concentrations are usually achieved within 10 minutes, so that no loading dose is required.

Dobutamine

This is a synthetic derivative of isoprenaline that acts primarily on β1-receptors in the heart (Sonnenblick et al, 1979). It exerts a more prominent inotropic and less prominent chronotropic action than isoprenaline, thereby increasing cardiac output with only a modest increase in heart rate. Its peripheral action is one of moderate vasodilatation via the stimulation of β2-receptors and it causes relatively little α1-mediated vasoconstriction. Dobutamine causes a modest fall in pulmonary wedge pressure. The effect on blood pressure depends on the balance between its effect on cardiac output and the reduction in systemic vascular resistance caused by vasodilatation. Usually there is a modest fall in blood pressure or little effect. Its most frequent dose-limiting effects are excessive tachycardia, arrhythmia and hypotension. As with other β1 agonists, tolerance or tachyphylaxis may develop during continuous administration (Unverferth et al, 1980). Dobutamine is probably the most commonly used inotrope in advanced heart failure. Its short half-life makes dose titration relatively easy. The typical dose range is 2–15 μg/kg/min but higher doses may be used, particularly in patients who have been receiving β-adrenergic receptor antagonists and during diagnostic studies.

Dopamine

The effects of dopamine are more complex and dose dependent (Poole-Wilson and Opie, 2005). At low doses (up to 2 μg/kg/min) stimulation of vascular dopaminergic receptors causes vasodilatation in the renal, splanchnic and coronary arteries and results in increased renal blood flow, glomerular filtration and natriuresis (Chatterjee and De Marco, 2003). At higher doses β1-stimulation becomes evident and above 5–10 μg/kg/min α1-receptor-mediated peripheral vasoconstriction also occurs. At these higher doses the cardiac output of heart failure patients may actually start to fall because of the adverse effect of an increased afterload on the failing left ventricle.

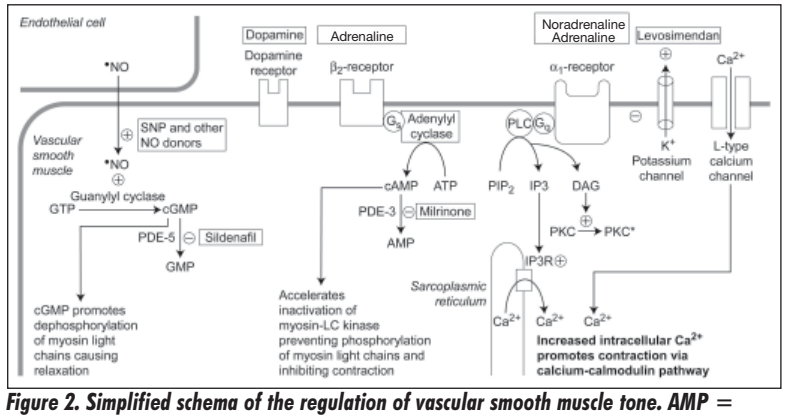


Figure 2. Simplified schema of the regulation of vascular smooth muscle tone. AMP = adenosine monophosphate; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; DAG = diacylglycerol; GMP = guanosine monophosphate; G_q = G_q coupling protein; GTP = guanosine triphosphate; IP3 = inositol triphosphate; IP3R = IP3 receptor; *NO = nitric oxide; PDE-3 = phosphodiesterase type-III; PDE-5 = phosphodiesterase type-V; PIP2 = phosphatidylinositol biphosphate; PKC = protein kinase C; PKC* = activated protein kinase C; PLC = phospholipase C; SNP = sodium nitroprusside.

Adrenaline

Adrenaline is the endogenous catecholamine that is secreted by the adrenal medulla. It acts on both β1 and β2 receptors producing both inotropic and chronotropic effects. It acts on peripheral α1 and β2 receptors causing vasoconstriction and vasodilatation respectively. At low doses (up to 0.2 μg/kg/min) β receptor stimulation predominates but at higher doses α-mediated vasoconstriction becomes evident and at even higher doses it is predominantly a vasoconstrictor (Poole-Wilson and Opie, 2005).

Noradrenaline

Noradrenaline is the peripheral sympathetic neurotransmitter. During intravenous administration its predominant haemodynamic effects are the result of α1-receptor stimulation causing peripheral arterial vasoconstriction and venoconstriction (Chatterjee and De Marco, 2003). Noradrenaline also stimulates β1 receptors and has an inotropic action. Noradrenaline is a powerful vasoconstrictor (vasopressor) and is not a first-line drug for the treatment of patients with heart failure. However, it is occasionally needed to reverse serious hypertension that can occur in heart patients treated with phosphodiesterase type III inhibitors, because of drug accumulation caused by deteriorating renal function (the pseudo-sepsis syndrome) (Chatterjee and De Marco, 2003).

Milrinone

Milrinone is the most commonly used type III phosphodiesterase inhibitor. It increases cardiac contractility and also causes peripheral vasodilatation by increasing cAMP levels. Short-term infusions of intravenous milrinone can be used to treat decompensated heart failure (Cuffe et al, 2002) although the subsequent outcome is not improved. Milrinone can cause a decrease in pulmonary arterial pressure, pulmonary capillary wedge pressure, systemic blood pressure and systemic and pulmonary vascular resistance while increasing cardiac output (Klocke et al, 1991). Its powerful vasodilator action makes it more effective in reducing pulmonary wedge pressure than dobutamine. Its inotropic effect persists in patients who have been treated with β-adrenergic receptor antagonist (Bristow et al, 2001). Milrinone is primarily excreted by the kidney and its half-life will become prolonged in patients with renal dysfunction and may be very long in patients treated with veno-venous haemofiltration (Larsson et al, 1986). Enoximone is another type III phosphodiesterase inhibitor with similar properties.

Levosimendan

Levosimendan is a calcium sensitizer whose use has been studied quite extensively in acute heart failure. However, it is currently not licensed in the UK. It has both inotropic and vasodilator actions. It is hepatically metabolized to active metabolites that are then excreted renally (Takahashi et al, 2000). The metabolites have long half-lives and so the administration of levosimendan must be limited to short-term treatment to prevent metabolite accumulation. Levosimendan improves systolic function without impairing diastolic function and decreases both system vascular resistance and pulmonary wedge pressure. It increases cardiac output without increasing oxygen demand.

Clinical applications in heart failure

The intravenous inotropes described here can improve haemodynamics in heart failure patients acutely but this has not been shown to translate into any medium or long-term clinical benefits. Indeed there was considerable evidence that chronic stimulation of the β1 adrenergic receptor/cAMP pathway increases mortality in heart failure. In the stages of heart failure where it can be tolerated, pharmacological blockade of the β1-receptor has been shown to improve survival (Bristow, 2000). Chronic oral therapy with drugs with β adrenergic properties and phosphodiesterase type III inhibitors has been associated with increased mortality (The Xamoterol in Severe Heart Failure Study Group 1990; Packer et al, 1991). Catecholamines are toxic to the cardiomyocyte (Mann et al, 1992). The initial clinical trials with levosimendan suggested that it may have a more beneficial effect (Follath et al, 2002; Moiseyev et al, 2002) but the recent SURVIVE study that was specifically powered to examine mortality differences in patients with acute heart failure failed to show any advantage over dobutamine (Mebazaa et al, 2007).

Inotropic therapy is associated with a number of limitations and adverse effects (see *Table 1* in article on acute heart failure and cardiogenic shock in this issue; p. 9). The commonest dose-limiting toxicities are excessive tachycardia, tachyarrhythmia and the induction of myocardial ischaemia in those with ischaemic cardiomyopathy (Chatterjee and De Marco, 2003).

Treatment of acute and decompensated heart failure

Inotropic therapy is useful in the emergency treatment of heart failure that is refractory to other treatments including diuretics and vasodilators, especially when the patient's condition is complicated by tissue hypoperfusion and organ dysfunction. It can also be used as a supportive therapy during diagnostic evaluation and before more definitive treatments such as cardiac transplantation or mechanical circulatory support. In this setting, it is sometimes used in combination with an intra-aortic balloon pump. Inotropes also have a role in the support of patients with cardiogenic shock (see article on acute heart failure and cardiogenic shock in this issue). It has been proposed that milrinone can also be used to facilitate the introduction of β-adrenergic antagonists in heart failure patients who would otherwise be intolerant of them. Lastly inotropes may have a role in the long-term management of left ventricular failure as part of the palliative care of patients who are not candidates for definitive treatment. Here improvement in quality of life is the goal rather than prolongation of life.

Postoperative care after cardiac surgery

Inotropes are frequently required during the early postoperative phase after cardiac surgery to improve temporary myocardial dysfunction (stunning) and support the patient during the recovery from the systemic effects of surgery and cardiopulmonary bypass (Breisblatt et al, 1990; Kloner et al, 1994).

Dobutamine stress imaging

The aim of pharmacological stress is to increase myocardial oxygen demand through a combination of inotropic and chronotropic effects. The drug used should produce effects that resemble those of dynamic exercise. In addition, the route of administration (central *vs* peripheral), side effects and safety must also be taken into account. For most purposes, the current agent of choice is dobutamine.

Dobutamine causes dilatation of the coronary resistance vessels which leads to an increase in coronary flow (Warltier et al, 1981) and a fall in perfusion pressure distal to coronary stenoses. Flow heterogeneity is produced (Meyer et al, 1976) with subendocardial blood

being redirected to the subepicardium. Dobutamine may also increase flow resistance at the site of a stenosis (Warltier et al, 1981). The increase in coronary flow with dobutamine has been reported as 2.1 times baseline at 10 μg/kg/min and 2.9 times baseline at 40 μg/kg/min (Krivokapich et al, 1993).

Dobutamine is the only sympathomimetic inotrope that can be safely infused into peripheral veins, as it has only a weak α-agonist effect. In a standard clinical protocol, dobutamine is infused at 5, 10, 20, 30 and 40 μg/kg/minute in 3-minute stages. Blood pressure and electrocardiogram are monitored throughout the test. If an insufficient physiological stress has been achieved even after reaching 40 μg/kg/min, atropine may be added. This is particularly relevant to the increasing number of patients taking beta-blockers as part of their drug regimen. Studies have shown that low-dose dobutamine stress echocardiography performed to assess myocardial viability is significantly less sensitive in the presence of beta-blockade (Zaglavara et al, 2002). In such patients, either a high-dose protocol must be used, or the patient's drug regimen must be tailored in order to safely reduce or discontinue beta-blockers, ideally for at least five drug half-lives before testing.

Most subjects also experience palpitation during the test. Minor, non-cardiac symptoms are almost universal and include tingling in the skin, particularly of the face and scalp, nausea, desire to urinate, shaking and lightheadedness. Ventricular and atrial premature beats are common occurring in approximately 15% and 10% respectively. Supraventricular tachycardia and atrial fibrillation may also occur. Non-sustained ventricular tachycardia occurs in about 5% of patients but is usually well tolerated. Hypotension may occur during dobutamine infusion; this is a result of systemic vasodilatation and it does not carry the same adverse prognosis as hypotension occurring during a dynamic exercise test (Rosamond et al, 1992). Dobutamine is safe in asthmatic patients. Dobutamine should be avoided in those with a history of ventricular tachycardia or with dynamic left ventricular outflow tract obstruction as a result of hypertrophic cardiomyopathy. The risk of major test-related cardiac complications (mainly ventricular arrhythmia) with dobutamine is 0.25–0.5% (Mathias et al, 1999).

Dobutamine stress has been used in conjunction with echocardiography (Sawada et al, 1991), myocardial perfusion imaging (Hays et al, 1993), and cardiac magnetic resonance (Nagel et al, 1999) in the diagnosis of ischaemic heart disease, to risk-stratify patients with known ischaemic heart disease, to predict recovery of function after regional or total revascularization (Pasquet et al, 2000) and to assess the severity of aortic stenosis and perioperative risk in the presence of significantly impaired left ventricular function (low-flow aortic stenosis) (Chambers, 2006). Excellent results have been demonstrated in comparisons with coronary angiography and exercise stress. Dobutamine has also been used with perfusion imaging (Elliott et al, 1991) and echocardiography (Poldermans et al, 1993) to determine cardiac risk before non-cardiac surgery, and at low dose levels it may identify viable myocardium by increasing wall thickening in regions with impaired function (Pierard et al, 1990). For the identification of hibernating myocardium and prediction of improved regional left ventricular function after revascularization, dobutamine stress echocardiography using a combined low-high dose regimen may be used. Improvement of myocardial wall motion and systolic thickening during low-dose dobutamine followed by deterioration at higher doses (the 'biphasic response') is highly specific for the prediction of recovery of function after revascularization (*Table 1*) (Afridi et al, 1997).

Practical aspects of inotropic therapy in heart failure

Because of the potential for adverse effects, inotropic therapy should only be considered when alternative therapies are contraindicated or not tolerated because of the severity of the heart failure. Whenever possible, a thorough diagnostic evaluation, including the use of echocardiography and right heart catheterization, should be done before commencing inotropic therapy. The choice of inotropic agent will be guided by the patient's haemodynamic state (heart rate, cardiac index, left and

Table 1. Regional left ventricular wall motion and thickening during dobutamine stress echocardiography: criteria for the assessment of myocardial ischaemia and viability

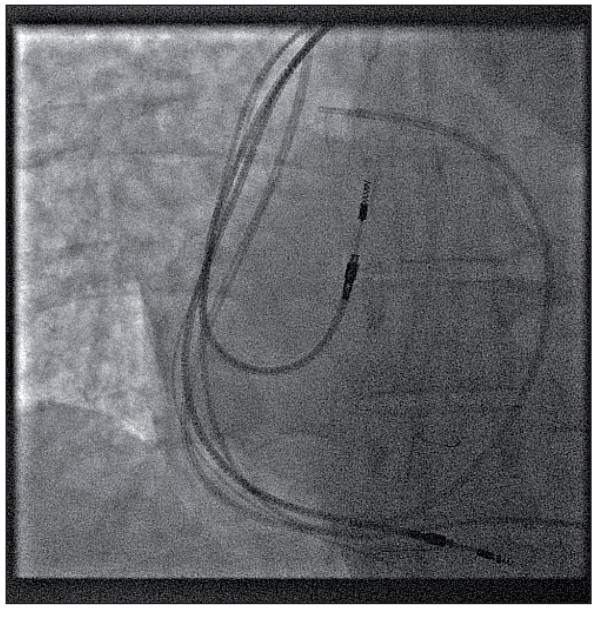
Baseline	Low-dose dobutamine	High-dose dobutamine	Type of response	Interpretation	Likelihood of functional recovery after revascularization
Normal	Increased	Further increase	Sustained improvement	Viable, normal myocardium	Not applicable
Normal	Increased	Deteriorated	Inducible wall motion abnormality	Ischaemia	Not applicable
Abnormal	No change	No change	No change	Non-viable	Very low
Abnormal	Improvement	Further improvement	Sustained improvement	Viable but not ischaemic	Low
Abnormal	Worse than rest or no change	Worse than at low dose or at rest	Worsening	Partially viable and ischaemic	Moderate
Abnormal	Improvement	Worse than at low dose	Biphasic	Viable and ischaemic	High

right filling pressures and systemic vascular resistance) as well as prior therapy (e.g. β-blockers). In addition, the phosphodiesterase inhibitors should be used with caution in patients with serious renal impairment. Inotropes agents should be administered with appropriate haemodynamic monitoring (heart rate, electrocardiogram, arterial pressure and usually central venous pressure); those with an α1-agonist (vasoconstrictor) effect must be given via a central line. Right heart catheterization with a pulmonary artery flotation catheter will enable changes in cardiac output and mixed venous oxygen saturation to be measured during therapy as well as changes in pulmonary capillary wedge pressure (*Figure 3*).

Common indications for inotropic therapy are symptomatic systemic hypotension as a result of low cardiac output or secondary organ dysfunction (especially hepatic or renal) or the occurrence of diuretic resistance in a volume-overloaded patient with a low cardiac output state.

It is often appropriate to begin with a trial of dobutamine therapy as the short half-life of this drug makes its effects rapidly reversible. Patients already receiving therapy with a β-adrenergic antagonist can be treated with higher doses of dobutamine but such patients often respond better to treatment with a phosphodiesterase inhibitor (Bristow et al, 2001). Patients with a particularly high filling pressure or vascular resistance may benefit most from an inodilator such as milrinone or levosimendan (if available). Treatment should be titrated to improve symptoms and organ dysfunction rather than seeking a complete normalization of haemodynamics (Jessup et al, 2006).

Figure 3. Fluoroscopic image showing a pulmonary artery flotation (Swan-Ganz) catheter being inserted into the pulmonary artery to monitor the haemodynamic response to inotropes. The patient also has a biventricular pacemaker in situ with atrial, right and left ventricular leads; an additional guidewire is also visible.

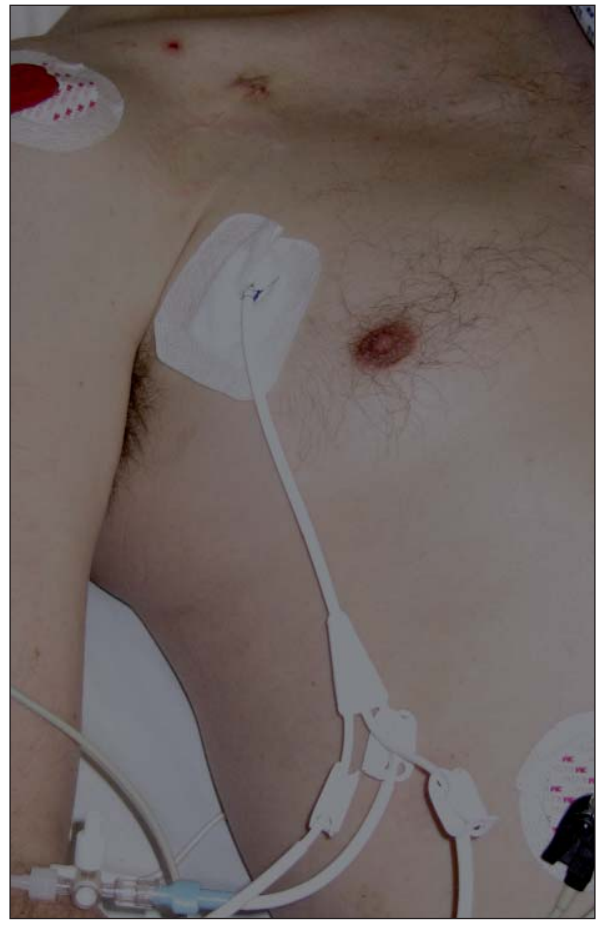


Line sepsis is a serious complication and patients who require prolonged inotrope therapy should have a tunnelled central line inserted to reduce the risk of infection (*Figure 4*). Most inotrope-dependent patients are relatively immobile and they should be anticoagulated to prevent the risk of venous thrombosis and embolism and also to prevent the development of thrombus within the right or left ventricles which may lead to pulmonary or systemic embolism respectively (*Figures 5* and *6*).

The response to inotrope therapy will depend on the degree of contractile reserve within the myocardium and is often inadequate. Furthermore, tolerance or tachyphylaxis to inotropes, particularly those drugs acting through the β1 receptor, may lead to diminishing therapeutic response with time. Under these circumstances, inotropic therapy may need to be supplemented by the use of an intra-aortic balloon pump or by mechanical circulatory support with a ventricular assist device (*Figure 7*).

Usually inotropic support should be seen as a short-term measure to allow recovery from temporary myocardial dysfunction, to allow an opportunity to correct other abnormalities, or to complete a diagnostic evaluation and plan for definitive therapy. When acute heart failure has been precipitated by another factor that has been resolved

Figure 4. Multi-lumen tunneled line that has been inserted via the right subclavian approach to reduce the risk of line-related sepsis during continuing inotropic support.



(e.g. arrhythmia, infection) or the cardiac function has improved (e.g. following revascularization or other cardiac surgery), the inotropes can usually be gradually withdrawn. However, where the underlying abnormalities cannot be corrected, heart transplantation or long-term mechanical circulatory support may need to be considered (although currently long-term mechanical circulatory support is not funded by the NHS in the UK). Inotropes frequently need to be continued in those awaiting heart transplantation (Brozena et al, 2004). Where definitive therapy is not possible, inotropes may sometimes need to be continued as a part of palliative care strategy (Lopez-Candales et al, 2004). The survival of truly inotrope-dependent patients receiving continuous long-term inotropic therapy is very poor (Stevenson et al, 2004). **BJHM**

Conflict of interest: none.

Figure 5. Echocardiographic image showing an off-axis view of the right ventricle of a patient with dilated cardiomyopathy which contains multiple thrombi.

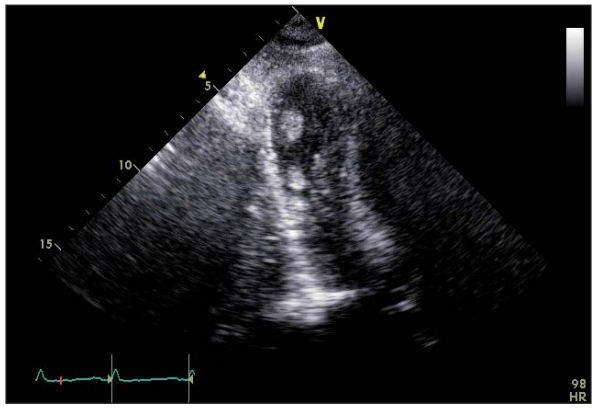


Figure 6. Oblique reformatted image of a contrast-enhanced computed tomography examination of a patient with dilated cardiomyopathy demonstrating a pulmonary embolus obstructing the right middle-lobe pulmonary artery leading to distal pulmonary infarction (with central necrosis) and surrounding pleural effusion. Also seen is a dilated left ventricular cavity which contains multiple thrombi.

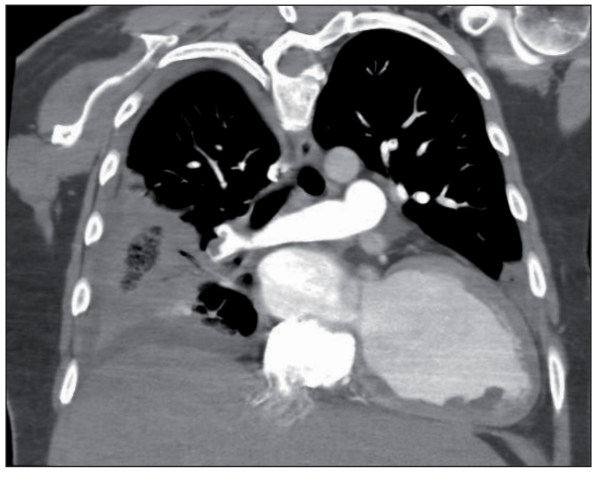


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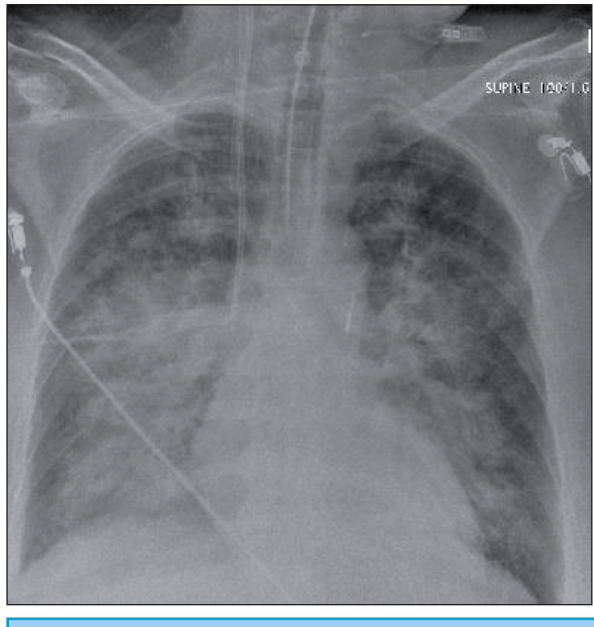
Figure 7. Portable chest radiograph of a patient with severe left ventricular failure. The patient is receiving inotropes via a central line; the tip of an intra-aortic balloon pump which is being used to off-load the left ventricle can be seen at the top of the descending thoracic aorta. The patient has been intubated and ventilated because of hypoxic respiratory failure caused by the pulmonary oedema.



KEY POINTS

- Inotropic agents can acutely increase cardiac output and improve other haemodynamic parameters in patients with heart failure.
- However, they do not improve and can actually worsen the long-term clinical outcome.
- Clinical indications for inotropes in heart failure include: emergency haemodynamic resuscitation, support after cardiac surgery, diagnostic imaging, bridging to a definitive therapy such as heart transplantation and also as part of palliative care.

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