Review

Bench-to-bedside review: Inotropic drug therapy after adult cardiac surgery – a systematic literature review

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Abstract

Many adult patients require temporary inotropic support after cardiac surgery. We reviewed the literature systematically to establish, present and classify the evidence regarding choice of inotropic drugs. The available evidence, while limited in quality and scope, supports the following observations; although all β-agonists can increase cardiac output, the best studied β-agonist and the one with the most favourable side-effect profile appears to be dobutamine. Dobutamine and phosphodiesterase inhibitors (PDIs) are efficacious inotropic drugs for management of the low cardiac output syndrome. Dobutamine is associated with a greater incidence of tachycardia and tachyarrhythmias, whereas PDIs often require the administration of vasoconstrictors. Other catecholamines have no clear advantages over dobutamine. PDIs increase the likelihood of successful weaning from cardiopulmonary bypass as compared with placebo. There is insufficient evidence that inotropic drugs should be selected for their effects on regional perfusion. PDIs also increase flow through arterial grafts, reduce mean pulmonary artery pressure and improve right heart performance in pulmonary hypertension. Insufficient data exist to allow selection of a specific inotropic agent in preference over another in adult cardiac surgery patients. Multicentre randomized controlled trials focusing on clinical rather than physiological outcomes are needed.

Introduction

Despite improvements in surgical technique and myocardial protection, pharmacological support for low cardiac output is often required during and after weaning from cardiopulmonary bypass (CPB) [1]. This acute deterioration in ventricular function may continue into the postanaesthesia care unit or intensive care unit (ICU). Because cardiac surgery is conducted in an increasingly aged population, with coexisting pathology, these patients are at increased risk for developing a low cardiac output syndrome (LCOS) during the postoperative period.

There is no consensus definition of what constitutes LCOS, but it would be reasonable to define it as a low cardiac output (cardiac index [CI] <2.4 l/min per m^2 is used as a criterion in some studies) with evidence of organ dysfunction, for example elevated lactate or urine output under 0.5 ml/hour for more than 1 hour. Such LCOS can persist for several hours to days, despite optimization of volume status, temporary pacing, or exclusion of mechanical factors (e.g. cardiac tamponade and mechanical assistance with intra-aortic balloon counter-pulsation). Causes are multifactorial but include myocardial ischaemia during cross-clamping, reperfusion injury, cardioplegia-induced myocardial dysfunction, activation of inflammatory and coagulation cascades, and unreversed pre-existing cardiac disease. LCOS can result in reduced oxygen delivery to vital organs [2]. Organ dysfunction and multiple organ failure are among the main causes of prolonged hospital stay after cardiac surgery, and this increases resource use and health care costs as well as increasing morbidity and mortality. Optimization of cardiac output and oxygen delivery may decrease morbidity and reduce length of stay [3].

CABG = coronary artery bypass grafting; CI = cardiac index; CPB = cardiopulmonary bypass; HR = heart rate; ICG = indocyanine green; ICU = intensive care unit; IMA = internal mammary artery; LCOS = low cardiac output syndrome; LVEF = left ventricular ejection fraction; MAP = mean arterial pressure; NO = nitric oxide; PDI = phosphodiesterase inhibitor; pHi = intramucosal pH; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance; SVI = stroke volume index.

Despite a wide range of available inotropic agents, no consensus exists regarding the treatment of LCOS post-CPB. This review examines the pharmacological options for providing inotropic support in the period after CPB and evaluates the literature systematically in order to establish, present and classify the available evidence regarding the use of inotropic drugs after cardiac surgery in adults. We do not discuss exclusive or mostly vasopressor drugs such as vasopressin and norepinephrine (noradrenaline).

Methods

We conducted a systematic Medline and PubMed search, over the period 1982–2003, using the following keywords: cardiac surgery, cardiopulmonary bypass, coronary artery bypass grafting, inotropic support, epinephrine, dopamine, dopexamine, dobutamine, amrinone, enoximone, milrinone and levosimendan. Agents considered to be primarily vasopressors (e.g. norepinephrine, arginine vasopressin and phenylephrine) and mechanical support (e.g. intra-aortic balloon counter-pulsation and assist devices) are not considered. For reasons of space and the likelihood that they would behave like other agents in their class, the more obscure phosphodiesterase inhibitors (PDIs; e.g. olprinone) not in common usage in the UK and Australia are not considered.

The bibliographies of articles identified through this methodology were also studied for reports that might have been missed in our initial searching of electronic reference libraries. Non-English language papers, animal studies, paediatric studies and *in vitro* studies are not included. Using this search strategy we identified 210 papers. This selection was further refined to 142 reports in which the agent in question was used for support of cardiac function or vital organ perfusion in patients who had undergone cardiac surgery. All articles in question were obtained.

Papers were selected and graded for quality of evidence according to the methodology of Cook and coworkers [4] (Table 1). Particular attention was given to the following issues regarding each agent in patients who have undergone cardiac surgery: what are the effects of each inotropic drug on systemic haemodynamics?; does the inotropic drug alter vital organ perfusion?; does the inotropic drug affect major clinical outcomes (e.g. time spent in hospital or ICU or requiring ventilation or artificial renal support) or survival?; and does the inotropic drug have any important side effects?

Data covering the application of each therapy were examined. Where possible, 'evidence-based' recommendations were developed.

Results

The results of our literature search are considered by pharmacological groups and agent. A full pharmacological profile of each agent is beyond the scope of the present review, but the proposed cellular mechanisms of action and receptor activation for each agent are schematically summarized in Fig. 1.

Table 1

Grading of responses to questions and levels of evidence

	Details
Levels of evidence	
I	Randomized trials with low α error (< 0.05) and β error (< 0.8)
II	Randomized trials with high α error or low power
III	Nonrandomized, concurrent cohort studies
IV	Nonrandomized, historic cohort studies
V	Case series
Grading of responses to questions	
A	Supported by at least two level I investigations
B	Supported by only one level I investigation
C	Supported by level II investigations only
D	Supported by at least one level III investigation
E	Supported by level IV or V evidence

Catecholamines

Natural and synthetic catecholamines have different haemodynamic effects because of their differential abilities to stimulate adrenergic receptors. Accordingly, each must be considered separately.

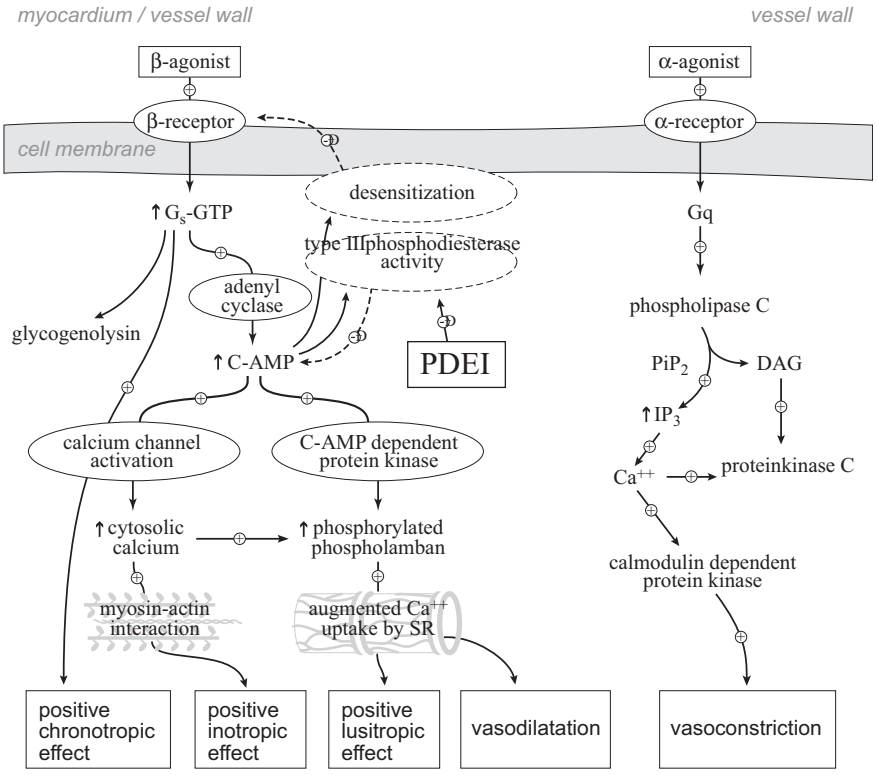
Epinephrine

Epinephrine (adrenaline) is a naturally occurring catecholamine that binds to both α- and β-receptor subgroups, with β effects predominating at low doses and α effects predominating at high dose. Fifteen reports relating to the use of epinephrine in cardiac surgical patients were retrieved using our search strategy. No study yielding 'level I' evidence (Table 1) was identified. Only one uncontrolled study, that by Gunnicker and coworkers [5], specifically investigated its effectiveness in LCOS.

In that report [5], epinephrine at a dose of 0.03 μg/kg per min produced significant increases in CI and heart rate (HR) of 24.1% and 14.1%, respectively, compared with placebo. HR was minimally affected in all studies except that of Gunnicker and coworkers, in which it increased by 14%. All studies recorded significant increases in mean arterial pressure (MAP) [6]. A recent observational study on the effects of 5 μg boluses in patients undergoing cardiac surgery [7] revealed a biphasic effect on systemic vscular resistance (SVR), with an initial increase followed by reduction.

Epinephrine has also been directly compared with amrinone, milrinone and dobutamine. Two small, randomized controlled trials [5,8] compared epinephrine with the PDI amrinone. In both studies, both drugs significantly increased CI from baseline. In the randomized, open-label trial conducted by Gunnicker and coworkers [5] in 20 patients with LCOS,

Figure 1



Schematic representation of the postulated mechanisms of intracellular action of catecholamines and phosphodiesterase inhibitors (PDEIs). Catecholamines activate β- or α-adrenergic receptors, which in turn are linked with different G regulatory proteins. The β-receptor is linked with a stimulatory Gs-guanidine triphosphate unit (Gs-GTP), which activates the adenyl cyclase system resulting in increased concentrations of cyclic AMP (C-AMP), which in turn activate calcium channels to lead to increased cytosolic calcium, which increases the contractility of the actin–myosin system through its binding with troponin C. Depending on the concentration of a C-AMP-dependent protein kinase, phospholambam is phosphorylated and the uptake of calcium by the sarcoplasmic reticulum (SR) is also affected. The concentration of C-AMP in the myocardium is also regulated by the activity of the type III phosphodiesterase enzyme. If this is inhibited by a PDEI, then C-AMP concentration rises, with effects on cytosolic calcium concentration. In the myocardium this leads to increased contractility, and in vascular smooth muscle to vasodilatation. The α-adrenergic receptor, on the other hand, activates a different regulatory G protein (Gq), which acts through the phospholipase C system and the production of 1,2-diacylglycerol (DAG) and, via phosphatidyl-inositol-4,5-biphosphate (PiP_2), of inositol 1,4,5-triphosphate (IP_3). IP_3 activates the release of calcium from the SR, which by itself and through the calcium–calmodulin dependent protein kinases influences cellular processes, which in vascular smooth muscle leads to vasoconstriction. DAG simultaneously activates protein kinase C, which leads to the phosphorylation of other proteins within the cell.

epinephrine produced a significantly greater increase in CI, HR and MAP than did amrinone. However, this was accompanied by significantly greater increases in myocardial workload and oxygen consumption. Lobato and coworkers [9] conducted a prospective, randomized, blinded trial comparing the myocardial relaxation effects of epinephrine with those of milrinone in patients undergoing elective coronary artery bypass grafting (CABG). Epinephrine (0.03 μg/kg per min) had no effect on left ventricular end-diastolic area, as measured using trans-oesophageal echocardiography, whereas milrinone significantly increased it by 15%. Two studies [10,11] compared epinephrine with dobutamine and found epinephrine to be less effective at increasing CI than dobutamine over what the authors considered a reasonable clinical range of doses (0.01–0.03 μg/kg per min for epinephrine and 2.5–5 μg/kg per min for dobutamine). However, dobutamine was associated with significantly more tachycardia for the same stroke volume index (SVI).

No studies were found regarding the effect of epinephrine on blood flow to vital organs. A prospective, randomized trial [12] showed that epinephrine produces lactic acidosis in some post-CPB patients.

Two randomized controlled trials, one of which used laser Doppler flowmetry, investigated the effect of epinephrine on internal mammary artery (IMA) graft flow [13,14]. Both of these studies found epinephrine to have no effect on IMA blood flow. An earlier crossover study of 28 patients [15],

using an electromagnetic flowmeter, had shown that epinephrine significantly increased flow through IMA and saphenous vein grafts.

No studies were found regarding the effect of epinephrine on major clinical outcomes or survival.

Dopamine

Dopamine is a naturally occurring catecholamine that binds to both α- and β-receptor subgroups, with β effects predominating at low dose and α effects predominating at high dose. Doses of 2–10 μg/kg per min are commonly used for inotropy, with doses of 1.5–3.0 μg/kg per min still used by some for renal protection ('renal dose') because of the binding of the drug to specific dopaminergic receptors in the kidney. Our literature search identified a total of 21 papers relating to the use of dopamine in cardiac surgical patients, all of which were retrieved.

None of these papers specifically compared the haemodynamic effects of dopamine with those of placebo. When the effects of dopamine on CI were compared with baseline data, dopamine at a dose of between 2.5 and 5.0 μg/kg per min produced significant increases in CI (range 16.3–57.9%). In all studies except one there was a significant rise in HR (range 4.5–45.7%).

At doses of up to 5 μg/kg per min, significant decreases in SVR (range 13.1–46.1%) were recorded. However, in 1982 Saloman and coworkers [16] conducted a prospective, randomized, blinded trial of 20 patients and found that increasing dopamine from 5.0 to 7.5 μg/kg per min caused significant increases in MAP and pulmonary vascular resistance (PVR) without increasing cardiac output. In a multicentre, prospective, blinded, randomized trial of 70 patients, Rosseel and coworkers [17] examined the use of dopamine in LCOS after cardiac surgery. The study compared dopamine with dopexamine in patients with CI below 2.2 l/min per m^2. Dopamine produced a 57.9% increase in CI compared with baseline. However, this was accompanied by a 25.5% increase in HR. Clinical efficacy (defined as CI > 2.5 l/min per m^2 and urine output > 0.5 ml/kg per hour) was significantly greater in the dopexamine group at 1–2 hours after commencement of the infusion and approached significance at other time points. Moreover, 63% of patients in the dopamine group had an adverse cardiac event (defined as arrhythmias, ischaemia and hypertension), which was significantly greater than with dopexamine.

Tarr and coworkers [18] compared the efficacies of dopamine, dobutamine and enoximone for weaning from CPB in a randomized trial of 75 patients. Nine of the 25 patients randomly assigned to dopamine failed to respond adequately, and the remaining 16 recorded an increase in CI of 25.7% but this was accompanied by an increase in HR of 44.3%, with little change in SVI. The CI in the dopamine treated group was significantly lower than in patients treated with either dobutamine or enoximone.

Dopamine has been studied extensively with regard to regional perfusion of the gut and kidney. Other than a case series of 15 patients reported by Davis and coworkers in 1982 [19], which suggested that low-dose dopamine might increase postoperative urine output and serum creatinine in CPB patients, several level II studies [20–23] have failed to provide any evidence to support its use. Jakob and coworkers [24,25] and Thoren and colleagues [26] conducted observational studies on the effect of dopamine on splanchnic perfusion using indocyanine green (ICG) dye clearance and laser Doppler flowmetry, respectively. They observed significant increases in splanchnic blood flow in the order of 27–36%. Two level II studies [27,28] failed to demonstrate any effect of dopamine on gastric intramucosal pH (pHi). A significant worsening in pHi associated with low CPB flow rate and dopamine was observed by Schneider and coworkers [29] in a randomized, double-blind, placebo-controlled trial ($n = 100$) conducted in 1998.

No data were found regarding the effect of dopamine on major clinical outcomes or survival.

Dobutamine

Dobutamine is a synthetic catecholamine and is a derivative of isoprenaline. It has strong affinity for β-receptors with little affinity for α-receptors because of the configuration of the terminal amine. Twenty-six studies investigating the effects of dobutamine in cardiac surgical patients were identified and retrieved. These studies are summarized in Table 2.

Administration of dobutamine in cardiac surgery patients produces a dose-dependent rise in CI. In the study conducted by Ensinger and coworkers [31], in which they compared dobutamine at 6.0 μg/kg per min with placebo, a significant increase in CI of 46% was recorded. Studies by Feneck and coworkers [2] and Tarr and colleagues [18], investigating the haemodynamic effects of dobutamine in LCOS, identified increases in HR in excess of 25%. Significant reductions in SVR (>40% in the study by Tarr and coworkers) were also recorded.

Romson and coworkers [32] conducted an observational study of 100 patients who had undergone cardiac surgery and were administered dobutamine at doses of 0–40 μg/kg per min, where tolerated, and compared these with 10 control patients who received no dobutamine. Those investigators found that HR increased by an average of 1.45 beats/min per μg/kg per min in patients who were able to receive the full dose (66 out of 100 patients). Of the patients who were unable to receive the full dose, more than half (52%) developed tachycardia greater than 85% of predicted maximum HR by age. Romson and coworkers

Table 2

Summary of literature search results for dobutamine

Ref.	*n*	Year	Study design	Level of evidence	Comparator	Dose (μg/kg per min)	End-points
[2][a,b]	120	2001	Multicentre, prospective, unblinded, randomized trial	II	Milrinone	10–20	Haemodynamic parameters
[26]	10	2000	Prospective, blinded, randomized, crossover study	III	Dopamine, dopexamine	2.7	Jejunal perfusion
[30][a]	64	2000	Prospective, blinded, randomized, controlled trial	II	Placebo, ranitidine	4.0	pHi
[31][a]	17	1999	Prospective, blinded, randomized, controlled trial	II	Placebo	6.0	Haemodynamic parameters, splanchnic blood flow
[32][a]	110	1999	Observational study	III	–	0–40	Haemodynamic parameters
[14]	30	1997	Prospective, blinded, randomized trial	II	Enoximone, epinephrine	3.0	IMA graft flow
[33][a,c]	20	1997	Prospective, unblinded, randomized trial	II	Enoximone	8.0	Haemodynamic parameters
[34][c]	20	1997	Prospective, blinded, randomized trial	II	Enoximone	5.0	Haemodynamic parameters
[35][a,b]	30	1996	Prospective, blinded, randomized trial	II	Enoximone	10.0	Haemodynamic parameters
[36][a,b]	28	1995	Prospective, unblinded, randomized controlled trial	II	Control	4.4	Haemodynamic parameters, pHi, ICG Clearance
[37][a,b]	10	1994	Prospective, blinded, randomized trial	II	Dopexamine	5.0–10.0	Haemodynamic parameters
[18][c]	75	1993	Prospective, blinded, randomized trial	II	Enoximone, dopamine	5.0	Haemodynamic parameters
[38][a,b]	16	1993	Prospective, unblinded, nonrandomized controlled trial	III	Sodium nitroprusside, control		Haemodynamic parameters ICG Clearance
[10]	52	1992	Observational study	III	Epinephrine	2.5–5.0	Haemodynamic parameters
[39][a,b]	30	1992	Prospective, unblinded, randomized trial	II	Amrinone	5–15	Haemodynamic parameters
[40]	10	1992	Observational study	III	Various dose ratios of dopamine/dobutamine	0–10.0	Haemodynamic parameters
[41][a]	20	1990	Prospective, unblinded, randomized trial	II	Enoximone	5.0	Haemodynamic parameters
[42][a]	20	1990	Prospective, unblinded, randomized trial	II	Enoximone	10.0	Haemodynamic parameters
[43][a,b]	40	1990	Prospective, unblinded, randomized trial	II	Enoximone	5–7	Haemodynamic parameters
[44][a]	50	1990	Prospective, unblinded, randomized trial	II	Enoximone	5.0	Haemodynamic parameters
[11][a]	16	1986	Prospective, unblinded, randomized, trial	II	Epinephrine	4.8	Haemodynamic parameters
[45][a,b]	9	1986	Sequential, cross-over study	III	Dopamine	5–10.0	Haemodynamic parameters
[16]	20	1982	Prospective, blinded, randomized trial	II	Dopamine	2.5–10.0	Haemodynamic parameters

[a]Postoperative support. [b]Cardiac index <2.5 l/min per m^2 or preoperative left ventricular ejection fraction <0.4. [c]Weaning from cardiopulmonary bypass. ICG, indocyanine green; IMA, internal mammary artery; pHi, intramucosal pH.

concluded that, in post-CPB patients, the dominant method of increasing CI was by increasing HR.

The Milrinone Multicentre Trial Group provided the most recent randomized controlled trial data concerning dobutamine [2]. That multicentre, randomized but not blinded study compared the haemodynamic effects of dobutamine with those of milrinone. A total of 120 patients with CI below 2.0 l/min per m^2 were studied and dobutamine was used at doses of 10–20 μg/kg per min. Dobutamine increased CI by 55% versus 36% with milrinone at 1 hour, and this effect was accompanied by a 35% increase in HR (versus 10% with milrinone) and a 31% increase in MAP (versus 7% with milrinone). Dobutamine was also associated with significantly higher incidences of hypertension and new atrial fibrillation (18% versus 5%; $P < 0.04$).

The randomized trial of 75 patients conducted by Tarr and coworkers in 1993 [18] identified no statistically significant difference in CI between enoximone and dobutamine (both drugs effectively increased CI). However, dobutamine produced significantly more tachycardia, and enoximone

produced significantly greater increases in SVI. A further five small randomized trials compared dobutamine with enoximone [33,41–44], but only one of these studies [44] demonstrated any difference between drugs, specifically a significantly greater increase in CI in the enoximone-treated group.

Two small randomized trials [34,39] compared dobutamine with amrinone and found no significant differences in haemodynamic effect. Dupuis and coworkers [39], however, did note an increase in incidence of arrhythmias in the dobutamine group, and 40% of patients treated with dobutamine suffered postoperative myocardial infarction versus none in the amrinone group ($P = 0.017$).

Regarding comparisons with other catecholamines, MacGregor and coworkers [37] conducted a randomized, blinded comparison of dopexamine and dobutamine in 10 patients undergoing CABG. No significant differences in haemodynamic variables were found, but there was a significantly greater incidence of supraventricular tachycardias in the dopexamine group. As mentioned above, Butterworth and coworkers [10] found no significant differences between epinephrine and dobutamine other than a significantly greater HR in the dobutamine-treated group.

Six studies investigated the effects of dobutamine on regional perfusion. The study by MacGregor and coworkers [37], outlined above, showed no difference in net sodium excretion or urinary output compared with dopexamine. The remaining studies investigated the effects of dobutamine on splanchnic blood flow. Four studies demonstrated significant increases in splanchnic blood flow as measured by ICG clearance [31,36,38] or laser Doppler flowmetry [26]. In studies in which pHi was measured, dobutamine had no effect [31,34] or decreased pHi [36].

We were unable to find any data relating to the effect of dobutamine on major clinical outcomes or survival.

Dopexamine

Dopexamine is a synthetic catecholamine with agonist activity at β_2-receptors and indirect action at β_1-receptors by inhibiting the uptake of endogenous catecholamines [46]. This agent is not available in some developed countries. Our literature search identified 20 papers investigating the effects of dopexamine in patients who had undergone cardiac surgery, all of which were retrieved.

Two randomized controlled trials [47,48] compared dopexamine with placebo. Hurley and coworkers [47] reported a study of 23 low-risk post-CABG patients in 1995. In that study, dopexamine at a dose of 2.0 μg/kg per min significantly increased CI by 41% and HR by 19%. SVR was also reduced by 45%. In their randomized, double-blind, placebo-controlled trial, Sherry and coworkers [48] similarly found significant increases in HR and CI over placebo (one patient was withdrawn from the study because of tachycardia).

We identified five studies investigating the effects of dopexamine in LCOS, the largest of which is the multicentre, randomized, blinded comparison of dopexamine with dopamine reported by Rosseel and coworkers [17]. In that study, the increased CI in the dopexamine group was accompanied by an increase in HR of 37%. As previously discussed, there was significantly greater efficacy and fewer adverse events in the dopexamine group (although 54% of the dopexamine group still suffered an adverse cardiac event in the form of arrhythmia or ischaemia).

McGregor and coworkers [37] conducted a prospective, randomized, blinded comparison of dopexamine with dobutamine ($n = 10$) in patients with LCOS after CABG. They found no difference between the agents other than the fact that tachycardia of greater than 120 beats/min was more common in the dopexamine group.

We were unable to find any studies comparing dopexamine with PDIs. One study, reported by Honkonen and coworkers [49], compared dopexamine with iloprost (a prostacyclin analogue) in a randomized, double-blind, crossover trial of 20 patients with total proximal occlusion of the right coronary artery. Dopexamine increased right ventricular ejection fraction significantly more than did iloprost at a dose of 0.68 μg/kg per min.

Eight studies investigated the effects of dopexamine on regional perfusion. A randomized, placebo-controlled trial of 44 patients undergoing CABG conducted by Berendes and coworkers [50] in 1997 found improvement in creatinine clearance in the dopexamine-treated groups. However, four subsequent small randomized trials [37,48,51,52] failed to provide any evidence that the use of dopexamine improves renal function or perfusion.

Berendes and coworkers [50] also assessed the effects of dopexamine on splanchnic oxygenation in a randomized, placebo-controlled trial of 44 patients with normal left ventricular ejection fraction (LVEF; >0.5) who received dopexamine at doses of 0.5, 1.0 and 2.0 μg/kg per min. There was no difference in hepatic venous oxygenation, and pHi decreased during and after CPB in all patients. A further three randomized controlled trials [28,53,54] concluded that dopexamine had no influence on pHi compared with dopamine or placebo. Dopexamine has also been shown to increase jejunal perfusion (as measured by laser Doppler flowmetry) and ICG dye clearance [55].

No studies were found relating to the effect of dopexamine on major clinical outcomes or survival.

Phosphodiesterase inhibitors

The cardiac effects of PDIs are characterized by positive inotropy and improved diastolic relaxation (lusitropy; Fig. 1). These agents also cause potent vasodilation, with reductions in preload, afterload and PVR. Acute tolerance is not a feature.

Amrinone

Amrinone (known as inamrinone in North America) is a bipyridine phosphodiesterase-III inhibitor. It is typically given as a loading dose of 0.75–1.5 mg/kg, followed by an infusion of 10 μg/kg per min. It has an elimination half-life of 3.5 hours in post-CPB patients [56]. Our literature search identified 27 papers, all of which were retrieved. One of these studies provided level I data regarding the use of amrinone in patients who have undergone cardiac surgery [57].

Lewis and coworkers [57] reported a prospective, randomized, placebo-controlled trial of 234 patients. In that study the amrinone group received a bolus of 1.5 mg/kg followed by an infusion of 10 μg/kg per min to wean from CPB. Phenylephrine or glyceryl trinitrate were also used to optimize perfusion pressure. Significantly fewer patients failed to wean in the amrinone group than in the control group (7% versus 21%; $P = 0.002$). Amrinone improved weaning success regardless of LVEF, although this benefit was only statistically significant in the group with a preoperative LVEF greater than 55%.

Another randomized controlled trial was undertaken by Ramsay and coworkers [58]. A total of 100 patients undergoing CABG were randomly assigned to receive a single bolus of 0.75 mg/kg amrinone (with no subsequent infusion) or saline before separation from CPB. Haemodynamic measurements were similar between the two groups at all times, but the amrinone group received a higher dose of phenylephrine. The authors of that study conceded that an insufficient amrinone dose might explain the lack of haemodynamic effect.

Of the remaining level II evidence available, Badner and coworkers [59] also conducted a randomized, blinded, placebo-controlled trial of 30 patients undergoing mitral valve replacement in which amrinone at 2.0 mg/kg or placebo was given before weaning from CPB. The amrinone group had a significant increase in CI (52% versus 10%) and decreases in SVR index (47% versus 10%), but there was no statistically significant difference in requirement for other inotropes or vasopressors between groups. Kikura and Sato [60] conducted a randomized, blinded comparison of amrinone, milrinone and placebo in 45 patients for weaning from CPB. Compared with placebo, amrinone significantly improved CI and SVI, and reduced dopamine requirements.

The remaining studies largely echo these findings. In two of these studies [61,62], however, more than 50% of patients in the amrinone group required concomitant infusions of phenylephrine to maintain MAP.

Two studies compared amrinone with milrinone [60,62] and one compared amrinone with enoximone [63]. None of these studies found significant differences in haemodynamic profiles. A further two randomized trials [5,8] compared amrinone and epinephrine; in both these studies amrinone produced a similar increase in CI and SVI, with significantly greater reductions in SVR.

Jenkins and coworkers [34] conducted a randomized, double-blind comparison of amrinone with dobutamine in 20 patients with severe pulmonary hypertension undergoing mitral valve replacement. Amrinone was associated with a reduction in pulmonary artery pressures and an increase in CI and right ventricular ejection fraction compared with dobutamine. Six patients in the dobutamine group suffered postoperative myocardial infarctions, as opposed to none in the amrinone group – a similar finding to that reported by Dupuis and coworkers [39].

Our literature search returned only one study relating to the effect of amrinone on vital organ perfusion. This was a prospective, randomized study of 29 patients, reported by Iribe and coworkers in 2000 [64]. That study compared the effects of amrinone, milrinone and olprinone on hepatic venous oxygen saturation. No significant change in hepatic venous oxygen saturation was demonstrated in the amrinone group ($n = 8$).

Although no studies used major clinical outcomes as primary end-points, the study by Lewis and coworkers [57], the largest randomized controlled trial, did not detect any statistically significant difference in length of ICU or hospital stay and mortality. The study by Butterworth and colleagues [61] similarly found no difference in mortality between amrinone and placebo groups.

Amrinone has been reported to impair coagulation because of a reduction in platelet count and function [65,66], and concerns over this have limited its use in some countries.

Enoximone

Enoximone is an imidazolone derivative phosphodiesterase-III inhibitor. It is typically used in doses of 0.5–1.5 mg/kg followed by an infusion of 5–10 μg/kg per min. It has a half-life of 2 hours in normal patients but this may be prolonged in patients with cardiac failure.

Of the 24 papers identified in our literature search, 19 investigated the effects of enoximone on systemic haemodynamics in post-CPB patients. Of these 19 papers, two were prospective, randomized, placebo-controlled trials. Boldt and coworkers [67,68] conducted both of these studies. The most recent of these studies [67] was

published in 2002 and is a prospective, randomized, blinded, placebo-controlled trial of 40 patients aged 80 years or older. The patients in that study received either enoximone (bolus dose of 0.5 mg/kg followed by an infusion of 2.5 μg/kg per min) or normal saline. Compared with placebo, enoximone-treated patients recorded a significant increase in CI (25.9%) and reduction in SVR (27.5%). No significant differences in HR and MAP were recorded. In 1992, Boldt and coworkers [68] conducted a further prospective, randomized, blinded, controlled study, again of 40 patients. Patients received either a single dose of enoximone 1.0 mg/kg or served as controls. Enoximone produced significant increases in CI (50%) and SVI (28.8%), and decreases in SVR (45.3%) and PVR (30.4%). No significant changes in HR and MAP were recorded. Oxygen delivery and consumption were also significantly higher in the enoximone group. Another study conducted by Boldt and coworkers [69] compared 40 patients who had received a single dose of enoximone 1.0 mg/kg with 40 historical controls. The enoximone-treated group required significantly less epinephrine, calcium and nitroglycerin than did the control group.

Several level II studies compared enoximone with other inotropic agents, both catecholamines and other phosphodiesterase-III inhibitors. One small, prospective, randomized trial failed to show any significant haemodynamic differences between amrinone and enoximone [62]. In the prospective, randomized, blinded trial conducted by Tarr and coworkers in 75 patients [18], only in the enoximone group were all patients successfully weaned from CPB, whereas three patients from the dobutamine group and nine from the dopamine group were withdrawn from the study because of inadequate response. The enoximone group exhibited a significantly lesser increase in HR and a greater increase in stroke index than did either the dopamine or dobutamine group, and also exhibited significantly a greater increase in CI and decrease in SVR in comparison with dopamine. Birnbaum and coworkers [70] conducted an earlier, prospective, randomized, blinded comparison of enoximone (two boluses of 0.5 mg/kg followed by an infusion of 5 μg/kg per min) with dopamine (3.0–4.0 μg/kg per min) in 20 patients and obtained similar results.

As previously mentioned, we were able to find a further five studies comparing enoximone with dobutamine. The largest of these studies is the previously cited study conducted by Zeplin and coworkers [44]. That study ($n = 50$) found that enoximone significantly increased CI in comparison with dobutamine.

Two small, randomized, controlled trials investigated the effect of enoximone on vital organ perfusion. These showed no effect on pHi and significant reductions in endotoxin release [71], interleukins and α_1-microglobulin in the enoximone-treated group [67]. Two randomized controlled trials ($n = 80$ and $n = 36$) [72,73] investigated the effects of enoximone on coagulation parameters and platelet count and function, and found no difference from control groups.

Finally, in a prospective trial [74] 88 elective CABG patients were randomly pretreated with enoximone, clonidine, enalalapril, or placebo. The enoximone-treated group exhibited lower troponin T and creatine kinase-MB levels compared with clonidine or placebo [74].

There are no data regarding the effect of enoximone on major clinical outcomes or survival other than those from the study conducted by Boldt and coworkers in 2002 [67], which found that tracheal extubation was performed significantly earlier in the enoximone-treated group.

Milrinone

Milrinone is a bipyridine methyl carbo-nitryl phosphodiesterase-III inhibitor. Loading doses of 20–50 μg/kg are typically given, followed by an infusion of 0.2–0.75 μg/kg per min. It has a half-life of 30–60 min.

Our literature search identified 29 papers relating to the use of milrinone in adults after cardiac surgical procedures. These papers are summarized in Table 3. Nineteen of the papers provided data on the haemodynamic effects of milrinone following cardiac surgery and 14 of the papers were prospective randomized trials.

Four prospective randomized trials [60,75,83,85] demonstrated the effectiveness of milrinone compared with placebo for weaning from CPB. In the study by Doolan and coworkers [85], all patients in the milrinone group ($n = 15$) were successfully weaned from CPB, as compared with only five out of the 15 in the group randomly assigned to placebo. In their prospective, blinded, randomized controlled trial, Yamada and coworkers [80] compared two groups of 24 patients with low and normal pre-CPB CI. In both these groups, the patients randomly assigned to milrinone exhibited significantly higher CI (46% in the low pre-CPB CI group) and significantly lower SVR (52% in the low pre-CPB CI group) than controls. HR was not significantly affected, but six out of 12 patients with a low CI required norepinephrine to maintain adequate systemic blood pressure. Similarly, Lobato and coworkers [83] found that a single dose of milrinone 50 mg/kg administered before separation from CPB significantly increased CI (43%) and decreased SVR and catecholamine requirement compared with placebo in 21 patients with pre-existing left ventricular dysfunction. Again, more patients in the milrinone group required vasopressor support. Kikura and Sato [60] obtained similar results with milrinone, and these effects were sustained into the first 24 hours after surgery.

Milrinone has been compared with catecholamines for postoperative support in LCOS, notably by the European

Table 3

Summary of literature search results for milrinone

Ref.	*n*	Year	Study design	Level of evidence	Comparator	Dose	End-points
[60][a]	45	2002	Prospective, blinded, randomized controlled trial	II	Amrinone/placebo	50 μg/kg then 0.5 μg/kg per min	Haemodynamic parameters
[75]	20	2002	Observational study	III	–	20 μg/kg	Haemodynamic parameters
[76]	20	2002	Observational study	III	–	50 μg/kg	Middle cerebral artery flow
[2][b,c]	120	2001	Multicentre, prospective, randomized trial	I	Dobutamine	50 μg/kg then 0.5 μg/kg per min	Haemodynamic parameters
[77][b]	20	2001	Prospective, blinded, randomized controlled trial	II	Control	0.5 μg/kg per min	Haemodynamic parameters
[78]	20	2001	Prospective, randomized, placebo-controlled trial	II	Placebo	0.25 μg/kg per min	pHi, inflammatory markers
[64][b]	29	2000	Prospective, randomized trial	II	Amrinone, olprinone	50 μg/kg	pHi, hepatic blood flow, oxygenation
[79][c]	45	2000	Prospective, randomized trial	II	NO	50 μg/kg then 0.5 μg/kg per min	Haemodynamic parameters; RVEF
[9]	20	2000	Prospective, randomized trial	II	Epinephrine	50 μg/kg	Haemodynamic parameters
[80]	48	2000	Prospective, blinded, randomized, placebo-controlled trial	II	Placebo	20 μg/kg then 0.2 μg/kg per min	Haemodynamic parameters
[13][b]	20	2000	Prospective, randomized trial	II	Epinephrine	50 μg/kg	IMA flow
[81]	24	1999	Prospective, randomized controlled trial	II	Control	50 μg/kg	Inflammatory markers
[27][b]	24	1999	Prospective, blinded, randomized, placebo-controlled trial	II	Dopamine, placebo	50 μg/kg then 0.375 μg/kg per min	pHi, $S_{HV}O_2$, endotoxin levels
[82][b]	22	1999	Prospective, randomized, placebo-controlled trial	II	Placebo	30 μg/kg then 0.5 μg/kg per min	Haemodynamic parameters pHi, $S_{HV}O_2$, inflammatory markers
[83][a,c]	21	1998	Prospective, blinded, randomized, placebo-controlled trial	II	Placebo	50 μg/kg	Haemodynamic parameters
[62][b]	44	1998	Prospective, multicentre, randomized trial	II	Amrinone	Two boluses of 25 μg/kg	Haemodynamic parameters
[84][b]	37	1997	Prospective, randomized controlled trial	II	Control	50/75 μg/kg then 0.5/0.75 μg/kg per min	Haemodynamic parameters
[85][a,c]	32	1997	Prospective, blinded, randomized, placebo-controlled trial	II	Placebo	50 μg/kg then 0.5 μg/kg per min	Haemodynamic parameters
[86][b]	24	1996	Observational study	III	–	25–75 μg/kg then 0.5 μg/kg per min for 1 hour	Haemodynamic parameters
[87][b]	29	1995	Observational study	III	–	25–75 μg/kg	Haemodynamic parameters
[88][a]	20	1995	Prospective, blinded, randomized trial	II	–	20 and 40 μg/kg then 0.5 μg/kg per min	Haemodynamic parameters
[89][b]	25	1994	Observational study	III	–	25, 50, 75 μg/kg or 0.5 μg/kg per min	Plasma concentration
[90][b,c]	12	1994	Observational study	III	–	50 μg/kg then 0.5 μg/kg per min	Plasma concentration
[91, 92][b,c]	99	1992	Observational study	III	–	50 μg/kg then	Haemodynamic parameters 0.375–0.75 μg/kg per min
[93][b,c]	24	1992	Observational study	III	–	50 μg/kg then 0.375–0.75 μg/kg per min	Haemodynamic parameters
[94][b,c]	35	1991	Observational study	III	–	50 μg/kg then 0.375–0.75 μg/kg per min	Haemodynamic parameters

[a]Weaning from cardiopulmonary bypass. [b]Postoperative support. [c]Cardiac index < 2.5 l/min per m^2 or preoperative left ventricular ejection fraction < 0.4.
IMA, internal mammary artery; NO, nitric oxide; pHi, intramucosal pH; RVEF, right ventricular ejection fraction; $S_{HV}O_2$, hepatic vein oxygen saturation.

Table 4

Summary of literature search findings

Agent	Total number of studies	'Level I' studies	'Level II' studies	Significant findings
Epinephrine	15	0	10	Increases CI with biphasic effect on SVR index. Produces rise in serum lactate
Dopamine	22	0	14	Increased SVR index at doses above 5.0 μg/kg per min. Less clinical efficacy than dobutamine, dopexamine, amrinone, or enoximone. Increased incidence of adverse cardiac events than with dopexamine
Dobutamine	23	0	18	Better efficacy than dopamine and epinephrine. Decreases SVR index. Tachycardia and tachyarrythmia (especially AF) associated with use. More ischaemic complications than with amrinone
Dopexamine	20		12	Greater tachycardia than with dobutamine. More efficacious and fewer adverse events than with dopamine.
Amrinone	27	1	13	Improved weaning from CPB. Improves CI and decreases SVR index with minimal effects on HR. Fewer ischaemic complications than with dobutamine. Reports of thrombocytopenia associated with use
Enoximone	24	0	15	Significant increase in CI without tachycardia. Decreases SVR index. As effective as dobutamine
Milrinone	27	0	17	Significant increase in CI without tachycardia. Decreases SVR index. As effective as dobutamine but less AF. Luistropic. Improves IMA graft flow. As effective as 20 ppm NO in pulmonary hypertension

AF, atrial fibrillation; CI, cardiac index; CPB, cardiopulmonary bypass; HR, heart rate; IMA, internal mammary artery; NO, nitric oxide; SVR, systemic vascular resistance.

Milrinone Multicentre Trial Group, which published the results of a randomized, open label, multicentre study of 120 patients treated with milrinone or dobutamine for LCOS after cardiac surgery [2]. The significant findings of this study are described above in the section on dobutamine.

As previously mentioned, two studies [60,62] compared amrinone with milrinone. Neither of these studies found significant differences in haemodynamic profiles.

Solina and coworkers [79] compared the use of milrinone with nitric oxide (NO) in cardiac surgery patients with pulmonary hypertension. Those investigators found that the effects of milrinone on right ventricular ejection fraction were comparable with NO at 20 ppm but significantly less effective than NO at 40 ppm.

Small randomized controlled trials [27,64,78,81] have examined the effects of milrinone on pHi, splanchnic blood flow and inflammatory markers. Two of these [78,81] suggested that the administration of milrinone may attenuate the fall in pHi associated with CPB and the increase in some markers of inflammation. The remaining studies showed no difference.

In a prospective, randomized study of 20 patients conducted by Lobato and coworkers [13], milrinone produced a 24% increase in grafted IMA flow, as measured by laser Doppler flowmetry. In an observational study of 25 patients [76] milrinone also increased cerebral blood flow, as measured by transcranial Doppler, after separation from CPB.

We were unable to find any data relating to the effect of milrinone on major clinical outcomes or survival in cardiac surgery patients.

Levosimendan

There is little published work on the use of the novel calcium sensitizer levosimendan in cardiac surgical patients with LCOS. Levosimendan is a new inodilator that exerts its inotropic effect by interacting with troponin C (the binding protein for calcium) to enhance the calcium sensitivity of cardiac myocytes.

In a multicentre, randomized, double-blind trial of 203 patients [95], the efficacy and safety of levosimendan were compared with those of dobutamine in severe low-output heart failure (the LIDO study). Levosimendan improved haemodynamic performance more effectively than did dobutamine in patients with severe, low-output heart failure, and there was significantly lower mortality in the levosimendan group. However, only 2–4% of the study population had postoperative cardiac failure. A recent uncontrolled pilot study in cardiac surgery patients with LCOS found that levosimendan increased CI and stroke volume while lowering pulmonary artery occlusion pressure [96].

Conclusion

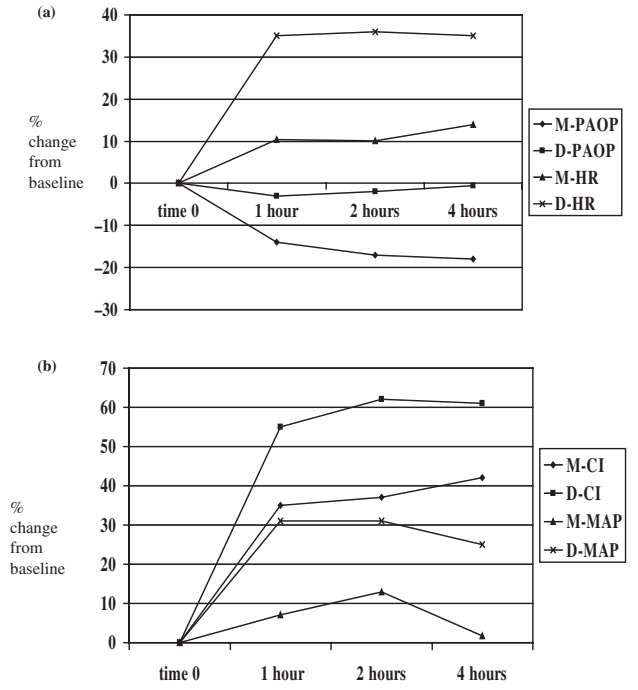
It is well recognized that myocardial dysfunction occurs after cardiac surgery. Because LCOS is common, contributes to morbidity and mortality, and increases length of ICU and hospital stay and costs, it is desirable to minimize its occurrence or attenuate its severity. A summary of the significant findings of our literature review are presented in Table 4. It is evident that there are two main classes of inotropic agents that should be used for support of cardiac output after cardiac surgery: catecholamines and PDIs (data for use of calcium sensitizers in this setting is scant). Moreover, all of these agents have been demonstrated to be effective at improving myocardial contractility or HR, or both. Although some reports in the literature suggest that catecholamines are more potent inotropic and chronotropic agents, serious drawbacks associated with their use include increased myocardial oxygen consumption, tachycardia, increased afterload and arrhythmias. β-Adrenergic receptors may also be downregulated in patients with pre-existing cardiac failure. This has led to interest in the use of phosphodiesterase-III inhibitors and, more recently, the calcium sensitizer levosimendan.

Studies investigating the use of PDIs in cardiac surgery have shown them to be potent inotropes, but vasodilation is a prominent feature of their use, and so concomitant administration of a vasoconstrictor such as norepinephrine or phenylephrine is often required. Such vasoconstrictor agents may or may not have adverse effects of their own. The effects of PDIs on HR appear to be minimal, and there is evidence to suggest that diastolic relaxation and flow through arterial grafts is improved. However, because of their pharmacokinetic profile, the time of onset and offset are longer (a loading dose is required) and they have the potential to accumulate in renal failure. These features can render the PDIs clinically less practical.

The effect of using either catecholamines or PDIs on major clinical outcomes or survival is unknown. We conducted an extensive literature search for data reported during the past 20 years relating to the use of inotropic agents in adult patients who have undergone cardiac surgery. Perhaps the most important finding of this review is the lack of large, double-blind, randomized controlled trials focusing on important clinical outcomes for drugs that are probably given to 250,000–500,000 people each year in western countries alone. Of course, there is overwhelming evidence that the agents considered in this review increase cardiac output, but the question of their comparative effects in the post-CPB heart and their effects on important clinical outcomes remains unclear. The available evidence is often not homogenous and is completely unsuitable for meta-analysis. Also, many of the data rely on physiological end-points, and there are clearly inherent pitfalls in this. Of 125 retrieved papers, only one 'level I' study was identified. The study by Feneck and coworkers [2] provides the only direct comparison between catecholamines and PDIs in patients with LCOS. A summary of haemodynamic changes between the milrinone group and the dobutamine group from the study is outlined in Fig. 2. Although that study included a reasonably large number of patients ($n = 120$), no convincing advantage was shown for either drug. Moreover, the observation period was only 4 hours and the outcomes were only physiological. This is disappointing because there are several theoretical advantages of PDIs over catecholamines: less tachycardia and myocardial oxygen consumption, improved diastolic relaxation, peripheral and pulmonary vasodilation, and increased IMA graft flow. On the other hand, such advantages are theoretically diminished by the need for vasopressor support.

Hoffman and coworkers recently reported the findings of the PRIMACORP study [97], a randomized, blinded, placebo-controlled trial that investigated the efficacy and safety of prophylactic milrinone in paediatric patients at risk for developing LCOS. Of the 239 patients investigated, high-dose milrinone (75 μg/kg per min followed by an infusion of 0.75 μg/kg per min) reduced the risk for LCOS by 48%. A

Figure 2



Summary of the haemodynamic changes that occur in the first 4 hours after treatment with milrinone or dobutamine [2]. All differences are presented as percentage change from baseline and are statistically significant. **(a)** The positive changes indicate an increase in heart rate (HR) and a decrease in pulmonary artery occlusion pressure (PAOP) with either milrinone (M) or dobutamine (D). **(b)** The changes represent the increases in cardiac index (CI) and mean arterial pressure (MAP) with milrinone (M) and dobutamine (D).

randomized controlled study of suitable statistical power must be conducted to compare fully the benefits of PDIs with those of dobutamine in adult cardiac surgical patients, with the focus on clinical rather than just physiological outcomes.

Following our systematic analysis of the literature, we believe that – despite the limitations of the data – some recommendations can be made, each with a particular level of evidence.

- Recommendation 1 (level C). β-Agonists or PDIs are more efficacious at increasing cardiac output than placebo for the treatment of LCOS after cardiac surgery. Beta-agonists are associated with a greater incidence of tachycardia and tachyarrhythmia. Administration of a vasoconstrictor is often required with PDIs.
- Recommendation 2 (level C). Catecholamines such as dopamine, epinephrine and dopexamine have no clear advantages over dobutamine and may be associated with a greater incidence of adverse effects. Epinephrine has been successfully used as salvage therapy.
- Recommendation 3 (level C). Administration of PDIs before separation from CPB increases the likelihood of successful weaning compared with placebo, and decreases the use of catecholamines during the postoperative period. Concerns regarding amrinone and thrombocytopenia have limited its use.
- Recommendation 4 (level C). There is no evidence that inotropes should be selected for their effects on regional perfusion.
- Recommendation 5 (level C). Administration of milrinone increases flow through arterial grafts.
- Recommendation 6 (level C). Milrinone and probably other PDIs reduce mean pulmonary artery pressure and improve right heart performance in pulmonary hypertension.

We believe that the field of clinical research into inotropic support for adult cardiac surgery has reasonably established the superiority of catecholamines and PDIs over placebo. However, insufficient evidence exists to guide the choice of one group of drugs versus the other. The role of the new calcium sensitizers remains unknown. It is biologically plausible that the use of catecholamines or PDIs may lead to different clinical outcomes and the clinical scenario of LCOS is relatively common, and so suitably powered, multicentre, randomized controlled trials should be a clinical research priority in adult cardiac surgery patients.

Competing interests

The author(s) declare that they have no competing interests.

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