Which inotropic agent is best for intensive care patients?

Some critically ill patients are judged by their clinicians to require infusion of a drug to increase or maintain cardiac output. Such pharmacological support is often given to patients after cardiac surgery, and to those with myocardial injury due to ischaemia, valvular dysfunction, pulmonary embolism or sepsis. It is broadly referred to as inotropic support, and the drugs used are loosely termed "inotropes". This is despite the fact that all of them also have effects on the peripheral vasculature, inducing either dilatation or constriction. In this issue of the Journal, Sterba and colleagues (*page 182*) report the use of one such agent — levosimendan — to assist with the management of patients who are difficult to wean from mechanical ventilation. This use of levosimendan raises interesting questions about the role of inotropic drugs in intensive care, but also makes one wonder whether the potential benefits depend on the specific agent, or represent a class effect. This, in turn, raises the question of which agent constitutes the "best choice" or the "best value" once the decision is made that an inotropic drug is needed.

Here, four intensivists take up my challenge to argue the case for a specific agent, with a limit of 400 words and five references. We hope this advocacy for particular interventions will help clinicians appreciate more clearly the pros and cons of a particular choice versus another. As shown below, there is no shortage of opinion and debate. Enjoy!

Rinaldo Bellomo, Editor
Critical Care and Resuscitation

The case for adrenaline

The autonomic nervous system regulates endogenous homeostatic responses through the interactions of the catecholamines, noradrenaline and adrenaline, with adrenoreceptors, which result in complex conformational changes in effector systems.[1] Both catecholamines have been used in clinical practice for the past 40 years, primarily as "rescue" drugs for acute shock states, with recommendations based on purported "selective" effects, where noradrenaline is regarded as a "vasopressor", and adrenaline as an "inotrope".

However, an increasing awareness by clinicians of the protean role of catecholamines as neuroendocrine hormones has seen a substantive change in practice, particularly in Australia and New Zealand. Catecholamines are used to defend vital organ perfusion rather than to treat shock, and it is common for intensive care patients, both with and without acute circulatory failure, to receive infusions of noradrenaline and/or adrenaline.

Unfortunately, current evidence supports neither approach. In 2004, a systematic review of higher-quality studies on patient-centred outcomes (comprising eight studies, with a total of 172 participants) concluded that no inotropes or vasopressors had been shown to be superior, either as sole agents or in combination.[2] The literature that forms the basis for current recommendations on haemodynamic management is dominated by non-blinded, case–control studies of the effects of various dosing regimens of inotropes/vasopressors, often in combination with synthetic drugs, on surrogate endpoints.[3] None of these are conclusive, and they are subject to substantial methodological and publication bias.

However, two recent studies provide the best methodological evidence for catecholamines in ICU patients to date. A French randomised controlled trial (RCT) demonstrated no difference in 28-day mortality in 330 patients with septic shock treated with either adrenaline or a combination of noradrenaline and dobutamine.[4] An Australian RCT demonstrated no difference in the achievement of a target mean arterial pressure in 280 patients assigned to receive either adrenaline or noradrenaline during their ICU admission.[5] Both studies demonstrated that adrenaline, while associated with transient lactic acidosis, was not associated with loss of haemodynamic efficacy or new organ dysfunction.

Therefore, based on current high-quality, investigator-initiated studies, the endogenous catecholamines, adrenaline and noradrenaline, represent the most efficacious vasoactive agent(s). This interpretation accords with the teleological responses outlined above, where exogenous infusions of catecholamines are used to augment endogenous neurohormonal systems.

Furthermore, as both drugs are off patent and inexpensive, adrenaline presents a cost-effective alternative in low-income countries where noradrenaline (or other synthetic inotropes) is unavailable, or its use is restricted by cost.

John A Myburgh, Professor
Division of Critical Care and Trauma, George Institute for International Health, and Department of Intensive Care Medicine, St George Hospital, Sydney, NSW.
Correspondence: j.myburgh@unsw.edu.au

1 Hein L. Adrenoceptors and signal transduction in neurons. *Cell Tissue Res* 2006; 326: 541-51.
2 Mullner M, Urbanek B, Havel C, et al. Vasopressors for shock. *Cochrane Database Syst Rev* 2004; (3): CD003709.
3 Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008; 36: 296-327.
4 Annane D, Vignon P, Renault A, et al. Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. *Lancet* 2007; 370: 676-84.
5 Myburgh JA, Higgins A, Jovanovska A, et al; the CAT Study investigators. A comparison of epinephrine and norepinephrine in critically ill patients. *Intensive Care Med* 2008; Jul 25. [Epub ahead of print].

The case for dobutamine

All inotropic agents can increase mortality.[1] Nonetheless, most clinicians accept a role for inotropes in low cardiac output states, and the debate is about the merits of the alternatives. In a choice between an unlicensed experimental agent, a difficult-to-titrate drug that causes hypotension, a cheap "one-drug-for-all-purposes" more at home in crises and the developing world, or a titratable agent that selectively increases cardiac output with few metabolic adverse effects, and reliably reduces symptoms,[1] most select dobutamine.[2] Dobutamine is the only recommended treatment for low cardiac output states in sepsis. More dobutamine is prescribed in Australia than any alternative (since 2004, 28× more than milrinone, and 1.5× more than adrenaline [P Clark, Hospira Australia, personal communication]). Why is this so?

Outcome benefit

A meta-analysis has shown that no conventional inotrope clearly improves outcome.[1] However, this meta-analysis excluded levosimendan. The LIDO trial[3] randomly allocated 203 patients to poorly titrated dobutamine, capped at 10 μg/kg/min, or levosimendan. Both drugs were given for 24 hours, but levosimendan's half-life is 80 hours, while dobutamine's is 2 minutes. Thirty-nine per cent of patients receiving dobutamine also received β-blockers. In this unfair comparison, patients receiving levosimendan had (marginally) improved haemodynamic status and 6-month survival. The SURVIVE trial[4] addressed these concerns: in 1327 patients, no survival difference was identified. Without evidence of comparative mortality benefit, this debate must concentrate on other features of each agent.

Physiological advantages

Dobutamine increases contractility and, more modestly, heart rate (β_1 effect), while causing vasodilatation (β_2) or vasoconstriction (α_1), depending on the vascular bed. It may increase or decrease blood pressure — unlike levosimendan and milrinone, which routinely necessitate the use of vasopressors, possibly negating their putative advantages. Like adrenaline, dobutamine increases myocardial oxygen demand, but offsets this by increasing perfusion. Some argue milrinone does not increase oxygen demand — a counterintuitive proposition contradicted by evidence.[5] Unlike adrenaline, dobutamine rarely causes lactic acidosis, and may cause less catabolism and insulin resistance. Dobutamine is arrhythmogenic, but possibly no more so than other agents are. In contrast to milrinone and levosimendan, it is highly titratable.

Logistic advantages

Dobutamine (at a daily cost per patient of A$20) is substantially cheaper than levosimendan (A$685) and milrinone (A$107). Adrenaline is only marginally cheaper (A$14) (Austin Hospital, August 2008). Most nurses are familiar with dobutamine, increasing safety. It is readily available in all Australian hospitals.

There is no evidence that choice of inotrope affects outcome, so cost and ease of use are deciding concerns. Most intensivists worldwide consequently choose the selective, titratable, familiar, effective and relatively inexpensive option: dobutamine.

Michael C Reade, Associate Professor
Intensive Care Unit, Austin Hospital, and University of Melbourne, Melbourne, VIC.
Correspondence: michael.reade@austin.org.au

1 Thackray S, Easthaugh J, Freemantle N, Cleland JG. The effectiveness and relative effectiveness of intravenous inotropic drugs acting through the adrenergic pathway in patients with heart failure — a meta-regression analysis. *Eur J Heart Fail* 2002; 4: 515-29.
2 Leone M, Vallet B, Teboul JL, et al. Survey of the use of catecholamines by French physicians. *Intensive Care Med* 2004; 30: 984-8.
3 Follath F, Cleland JG, Just H, et al. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. *Lancet* 2002; 360: 196-202.
4 Mebazaa A, Nieminen MS, Packer M, et al. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE randomized trial. *JAMA* 2007; 297: 1883-91.
5 Chiu WC, Kedem J, Weiss HR, et al. Milrinone, a cyclic AMP-phosphodiesterase inhibitor, has differential effects on regional myocardial work and oxygen consumption in experimental left ventricular hypertrophy. *Cardiovasc Res* 1994; 28: 1360-5.

The case for levosimendan

Inotropic agents exert favourable haemodynamic effects by improving cardiac contractility. However, most of these agents have the potential to increase myocardial oxygen consumption and ventricular arrhythmias, and many have shortened the survival of patients with heart failure. The cost of uncoupling myocardial oxygen supply and demand with increasing heart rate creates justifiable concerns, particularly in patients with known or suspected myocardial ischaemia. Tachycardia may often be best avoided by augmenting contractility, and therefore the chronotropic effects of these agents may not manifest if the inotropic benefit is realised.

Levosimendan is a positive inotropic agent with direct vasodilating actions and is therefore called a novel inodilator; it improves cardiac contractility by sensitising troponin C to calcium (calcium sensitiser).[1] This inotropic effect is independent of cyclic-AMP production, thereby leaving intracellular Ca^{2+} concentration unaffected. Hence, levosimendan promotes neither ventricular arrhythmias nor relevant increases in myocardial oxygen consumption. Its global vasodilating and anti-ischaemic properties are ascribed to the activation of potassium channels in vascular smooth muscle cells and mitochondria. Levosimendan may also help prevent apoptosis by preserving mitochondrial function, thus offering a degree of protection against programmed cell death.

Two large prospective trials that evaluated the efficacy of levosimendan in patients hospitalised for acute decompensated heart failure showed an early benefit when is was used in addition to standard therapy versus placebo in REVIVE-II,[2] and fewer deaths versus dobutamine in SURVIVE.[2] However, SURVIVE failed to meet its primary goal of reducing mortality by 25% at 6 months — a goal described by the investigators as "ambitious". It is dangerous to extrapolate the results of the SURVIVE study, as it targeted only patients with decompensated left ventricular failure. Morelli et al[3] showed that, in patients with septic shock, levosimendan was superior to dobutamine in increasing myocardial performance and improving blood flow to various tissues, with concomitant improvement in oxygen delivery. Morelli et al[4] also demonstrated that the use of levosimendan in patients with early acute respiratory distress syndrome and right ventricular dysfunction improved the latter by decreasing right ventricular afterload. Kerbaul et al[5] showed that levosimendan restores right ventricle–vascular coupling in animals challenged with massive pulmonary embolism, thereby increasing right ventricular contractility and pulmonary vascular impedance. Levosimendan has been successfully used in cases of refractory shock and massive pulmonary embolism.

Therefore, levosimendan is the inotropic agent of choice in intensive care patients.

Bart L De Keulenaer, Intensivist
Fremantle Hospital, Fremantle, WA.
Correspondence: bdekeul@hotmail.com

1 Pinto BB, Rehberg S, Ertmer C, Westphal M. Role of levosimendan in sepsis and septic shock. *Curr Opin Anaesthesiol* 2008; 21: 168-77.
2 Cleland JG, Freemantle N, Coletta AP, Clark AL. Clinical trials update from the American Heart Association: REPAIR-AMI, ASTAMI, JELIS, MEGA, REVIVE-II, SURVIVE, and PROACTIVE. *Eur J Heart Fail* 2006; 8: 105-10.
3 Morelli A, De Castro S, Teboul JL, et al. Effects of levosimendan on systemic and regional hemodynamics in septic myocardial depression. *Intensive Care Med* 2005; 31: 638-44.
4 Morelli A, Teboul JL, Maggiore SM, et al. Effects of levosimendan on right ventricular afterload in patients with acute respiratory distress syndrome: a pilot study. *Crit Care Med* 2006; 34: 2287-93.
5 Kerbaul F, Gariboldi V, Giorgi R, et al. Effects of levosimendan on acute pulmonary embolism-induced right ventricular failure. *Crit Care Med* 2007; 35: 1948-54.

The case for milrinone

Milrinone is an inhibitor of phosphodiesterase type III. It increases intracellular cyclic-AMP levels and hence elevates calcium concentrations. The resultant increase in myocardial contractility and associated peripheral vasodilatation (the "inodilator" effect) augments cardiac output through higher stroke volume. Because its mechanism of action is distinct from that of catecholamines, it remains effective in patients receiving β-blockers or with down-regulation of cardiac adrenoreceptors, as occurs in long-standing cardiac failure.[1]

Compared with β-agonists, milrinone has a lesser effect on heart rate[2] and fewer undesirable metabolic associations (eg, the increased blood lactate levels associated with adrenaline). Conventional inotropes tend to increase myocardial oxygen consumption, but this may be less of an issue with milrinone.[2,3] Other benefits include reliable lowering of filling pressures,[4] and reductions in pulmonary vascular resistance compared with β-agonists.[5] Milrinone has a favourable safety profile. Serious arrhythmias have been reported, but are seldom seen in clinical practice. The

only common adverse effect is hypotension resulting from excessive vasodilatation. Major reductions in arterial pressure can be avoided by using smaller loading doses in patients whose condition is unstable, and by carefully titrating infusion rates according to measured cardiac output and blood pressure. The ability to titrate milrinone dose in unstable patients is a major advantage compared with levosimendan, which has a much longer duration of action. Renal impairment necessitates dosing modification, as the kidney is the major route of elimination.

Most patients given milrinone are likely to require vasoconstrictor therapy, as peripheral vasodilatation may be excessive at doses sufficient to achieve the desired inotropic effects. In general, the dose of vasoconstrictor necessary to offset the excess vasodilatation is not great, and a valuable synergistic effect may occur when milrinone is administered concurrently with the vasoconstrictor noradrenaline.[1] Noradrenaline's slight β-adrenergic effects can be of considerable benefit during milrinone therapy, contributing to greater improvements in cardiac performance.

Milrinone is an effective inotropic agent for short-term use in the ICU, and current pricing makes it affordable. It promptly and reliably improves cardiac output, is reasonably titratable and can be used in combination with catecholamines if desired. It has few clinically significant side effects, and no major interactions with other drugs commonly used in the critically ill. While many clinicians may consider it an unfamiliar "boutique" drug, milrinone should be considered as first-line therapy for low cardiac output states requiring pharmacological support in the ICU.

Stephen J Warrillow, Intensive Care Specialist
Department of Intensive Care, Austin Health, Melbourne, VIC.
Correspondence: Stephen.Warrillow@austin.org.au

1 Yamada T, Takeda J, Katori N, et al. Hemodynamic effects of milrinone during weaning from cardiopulmonary bypass: comparison of patients with a low and high pre-bypass cardiac index. *J Cardiothorac Vasc Anesth* 2000; 14: 365-6.
2 Petersen JW, Felker GM. Inotropes in the management of acute heart failure. *Crit Care Med* 2008; 36: S106-11.
3 Monrad ES, Baim DS, Smith HS, Lanoue AS. Milrinone, dobutamine, and nitroprusside: comparative effects on hemodynamics and myocardial energetics in patients with severe congestive heart failure. *Circulation* 1986; 73 (3 Pt 2): III168-74.
4 Yamani MH, Haji SA, Starling RC, et al. Comparison of dobutamine based and milrinone based therapy for advanced decompensated congested heart failure: Hemodynamic efficacy, clinical outcome, and economic impact. *Am Heart J* 2001; 142: 998-1002.
5 Eichhorn EJ, Konstam MA, Weiland DS, et al. Differential effects of milrinone and dobutamine on right ventricular preload, afterload and systolic performance in congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1987; 60: 1329-33. ❑