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Understanding the differences among inotropes

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Introduction

Inotropes are indicated to restore cardiac output (CO) in the presence of signs of tissue hypoperfusion despite optimization of volume status, oxygenation and haematocrit level. Inotropes, especially catecholamines, cannot be widely used as they are associated with numerous and frequent short- and long-term adverse events. However, despite clear indications by the most prominent international societies of intensive care and cardiology to restrict their use, the current use of catecholamines is very frequent [1].

The 2012 European Society of Cardiology (ESC) Heart Failure Guidelines and the 2014 European Society of Intensive Care Medicine (ESICM) Consensus on shock recommend that "inotropic agents should be added when the altered cardiac function is accompanied by a low or inadequate CO and signs of tissue hypoperfusion persist after preload optimization" (Level 2; QoE low) [2].

Furthermore, the 2014 ESICM Consensus on shock indicated that evaluation of CO and cardiac function, by any means, becomes crucial when deciding on whether inotropic agents have a place in the therapy of a given patient and in evaluating the haemodynamic impact of those therapeutic interventions [2].

We provide a brief overview on current and future inotropic agents with a special focus on the pharmacological and clinical characteristics of the different classes (Table 1). The "ideal" inotropic agent should improve stroke volume without increasing myocardial oxygen consumption or causing arrhythmias, should ameliorate diastolic function and upstream congestion, should have a short half-life so as to be easily titratable and should have positive effects on long-term outcome. The "ideal" agent has not yet been found.

Pharmacology

Catecholamines and phosphodiesterase (PDE) III inhibitors

Both substance classes enhance the power of the contractile apparatus by increasing the intracellular cyclic adenylate monophosphate (cAMP) levels, which consecutively stimulates calcium release form the sarcoplasmatic reticulum of the cardiac myocytes. Catecholamines increase the production of cAMP by activating adenylate cyclase through beta-adrenergic receptors; PDE III

Table 1 Available and future inotropic agents

	Dobutamine	Adrenaline	Milrinone	Levosimendan	Omecamtiv
Substance class	Catecholamines	Catecholamines	PDE III inhibitor	Calcium sensitizer	Myosin activator
Mechanism of inotropic effect	Beta-adrenergic receptor-mediated increase of cAMP synthesis	Beta-adrenergic receptors-mediated increase of cAMP synthesis	Decreased breakdown of cAMP through inhibition of PDE III	Enhanced troponin C sensitivity to intracellular calcium	Increased actin–myosin cross-bridging by direct stimulation of cardiac myosin
Half-life	2–3 min	2 min	2 h	1 h, metabolite (OR-1896) up to 80 h	19 h
Common IV infusion (mcg/kg/min)	2–20	0.01–0.10	0.375–0.750	0.05–0.20	Under investigation
Frequent adverse effects	Hypotension (14 %), ventricular arrhythmia (7 %), chest pain (7 %), atrial fibrillation (6 %) [15]	Supraventricular tachycardia (12 %), ventricular arrhythmia (7 %), acute coronary events (3 %) [12]	Hypotension (7 %), atrial fibrillation (3 %), ventricular arrhythmia (2–4 %); increased events in ischaemic heart disease [3]	Hypotension (15 %), atrial fibrillation (9 %), ventricular arrhythmia (8 %), headache (8 %) [15]	Under investigation

inhibitors, on the other hand, increase the cAMP levels by inhibiting the enzyme which catalyses the breakdown of cAMP.

Dobutamine and adrenaline (or epinephrine) are the two most commonly used inotropic catecholamines: they have positive inotropic and chronotropic effects and increase myocardial oxygen consumption. They have a very short half-life and are administered as continuous intravenous infusions. Dobutamine is a synthetic agonist of beta1- and beta2-adrenergic receptors. Adrenaline, a natural occurring catecholamine, stimulates alpha1-, beta1- and beta2-adrenergic receptors. In contrast to dobutamine, which causes peripheral vasodilation through beta2-adrenergic receptor stimulation, adrenaline causes alpha1-mediated peripheral vasoconstriction, which increases cardiac afterload. Prolonged infusion of catecholamines is associated with tolerance (tachyphylaxis) due to downregulation of adrenergic receptors.

Milrinone, the most commonly used PDE III inhibitor, undergoes renal clearance and is administered by a continuous infusion. Compared to dobutamine, milrinone causes less pronounced tachycardia but more profound hypotension. PDE III inhibitors markedly reduce cardiac filling pressures as well as pulmonary vascular resistances. The latter makes milrinone particularly attractive for the treatment of patients with concomitant pulmonary arterial hypertension. Moreover, PDE III inhibitors act independently from adrenergic receptors and therefore these drugs are suitable for simultaneous administration with beta-blockers. The use of cAMP-mediated inotropic substances is associated with increased supraventricular and ventricular arrhythmic events and reduced long-term survival, in particular in patients with coronary artery disease [3].

Levosimendan

Levosimendan improves myocardial efficiency without either increasing myocardial oxygen demand or impairing ventricular relaxation. Levosimendan enhances troponin C sensitivity to intracellular calcium and prolongs the actin–myosin cross-bridge association rate [4]. As a cAMP-independent agent, levosimendan is well indicated in patients on beta-blockers. Moreover, levosimendan opens ATP-sensitive potassium channels of vascular smooth muscle cells causing peripheral vasodilatation, decreasing the cardiac afterload and leading to a further increase of CO (inodilatory properties). Levosimendan has modest positive chronotropic effects. At high doses, levosimendan also acts as a PDE III inhibitor, and, possibly for that reason, most clinicians start with a continuous infusion (without bolus dose) slowly increasing the rate. Other beneficial pleiotropic effects of levosimendan have been described in recent years, but are not discussed in detail here.

Novel inotrope: omecamtiv

Recently, omecamtiv, the first selective cardiac myosin activator, has been studied. Omecamtiv directly stimulates the actin–myosin cross-bridging, thereby increasing the contractile force of the sarcomere and, in contrast to catecholamines and PDE inhibitors, has no effect on intracellular calcium concentrations [5]. Therefore no increased myocardial oxygen consumption or arrhythmias appear to be associated with the use of this drug [6].

Clinical use

As stated above, inotropes are only indicated to restore cardiac function in the presence of signs of tissue hypoperfusion. Catecholamines and levosimendan seem to have roughly similar short-term effects on CO. However, other beneficial effects are expected but are as yet uncertain; for example, a myocardial protective effect of levosimendan is under investigation for cardiosurgical patients. We therefore provide here expert opinion rather than results from solid trials that are indeed very much needed.

Low cardiac output state and cardiogenic shock

Both share impaired cardiac index below 2.0 l/min/m^2 and increased ventricular filling pressures. Cardiogenic shock also shows signs of hypoperfusion. No data favour the use of one inotrope compared to another, though PDE III inhibitors or levosimendan should be favoured in patients on beta-blockers [7] and levosimendan in patients with decompensated chronic heart failure or for postoperative cardiac stunning [8]. Positive long-term effects of levosimendan on mortality are still controversial [9]. For the management of cardiogenic shock, recent data suggest that the combination of short-term use of positive inotropes and vasopressors should be favoured compared to vasopressors alone [10].

Septic shock

During septic shock, inotropes are indicated in case of impaired cardiac function and CO. It is worth mentioning that, when present, myocardial depression in septic shock is always found in a patient already with vascular dysfunction and need of vasopressors. Furthermore, sepsis-induced myocardial depression is reversible and, if needed, an inotrope should be given for 3–5 days [11]. In case of prolonged need of inotrope, one should search for another mechanism of cardiac dysfunction than sepsis. Of note, the 2014 ESICM consensus recommend not to give inotropes for isolated impaired cardiac function (Level 1, QoE moderate) [2]. No significant differences have been found comparing dobutamine plus norepinephrine versus epinephrine alone in septic shock [12]. In a recent trial, dobutamine failed to improve peripheral perfusion despite improving haemodynamic parameters [13]. Milrinone can be alternatively used to increase CO, especially in patients treated with beta-blockers, but aggravation of hypotension is a limiting adverse effect. Levosimendan has been successfully used in patients with septic shock [14], although hypotensive effects caused by peripheral vasodilation may limits its use.

In summary, inotropes are indicated in case of evidence of impaired CO and cardiac function in presence of signs of tissue hypoperfusion. All inotropes have roughly similar short-term effect on CO. Other short and most importantly long term beneficial effects need solid evidence.

Conflicts of interest MA has no conflict of interest to declare. AM is member of advisory boards for Bayer, Cardiorentis and The Medicines Company and received lecture fees from Alere, Edwards, Orion, Novartis, Vifor and Thermofisher.

References

1. Mebazaa A, Parissis J, Porcher R et al (2011) Short-term survival by treatment among patients hospitalized with acute heart failure: the global ALARM-HF registry using propensity scoring methods. Intensive Care Med 37:290–301. doi: 10.1007/s00134-010-2073-4
2. Cecconi M, De Backer D, Antonelli M et al (2014) Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. Intensive Care Med 40:1795–1815. doi: 10.1007/s00134-014-3525-z
3. Felker GM, Benza RL, Chandler AB et al (2003) Heart failure etiology and response to milrinone in decompensated heart failure: results from the OPTIME-CHF study. J Am Coll Cardiol 41:997–1003. doi: 10.1016/S0735-1097(02)02968-6
4. Papp Z, Édes I, Fruhwald S et al (2012) Levosimendan: molecular mechanisms and clinical implications: consensus of experts on the mechanisms of action of levosimendan. Int J Cardiol 159:82–87. doi:10.1016/j.ijcard.2011.07.022
5. Hasenfuss G, Teerlink JR (2011) Cardiac inotropes: current agents and future directions. Eur Heart J 32:1838–1845. doi: 10.1093/eurheartj/ehr026
6. Cleland JGF, Teerlink JR, Senior R et al (2011) The effects of the cardiac myosin activator, omecamtiv mecarbil, on cardiac function in systolic heart failure: a double-blind, placebo-controlled, crossover, dose-ranging phase 2 trial. Lancet 378:676–683. doi: 10.1016/S0140-6736(11)61126-4

7. Mebazaa A, Nieminen MS, Filippatos GS et al (2009) Levosimendan vs. dobutamine: outcomes for acute heart failure patients on beta-blockers in SURVIVE. Eur J Heart Fail 11:304–311. doi:10.1093/eurjhf/hfn045
8. Mebazaa A, Pitsis AA, Rudiger A et al (2010) Clinical review: practical recommendations on the management of perioperative heart failure in cardiac surgery. Crit Care 14:201. doi: 10.1186/cc8153
9. Koster G, Wetterslev J, Gluud C et al (2014) Effects of levosimendan for low cardiac output syndrome in critically ill patients: systematic review with meta-analysis and trial sequential analysis. Intensive Care Med. doi: 10.1007/s00134-014-3604-1
10. Pirracchio R, Parenica J, Resche Rigon M et al (2013) The effectiveness of inodilators in reducing short term mortality among patient with severe cardiogenic shock: a propensity-based analysis. PLoS One 8:e71659. doi: 10.1371/journal.pone.0071659
11. Rudiger A, Singer M (2013) The heart in sepsis: from basic mechanisms to clinical management. Curr Vasc Pharmacol 11:187–195
12. Annane D, Vignon P, Renault A et al (2007) Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. Lancet 370:676–684. doi:10.1016/S0140-6736(07)61344-0
13. Hernandez G, Bruhn A, Luengo C et al (2013) Effects of dobutamine on systemic, regional and microcirculatory perfusion parameters in septic shock: a randomized, placebo-controlled, double-blind, crossover study. Intensive Care Med 39:1435–1443. doi: 10.1007/s00134-013-2982-0
14. Morelli A, De Castro S, Teboul J-L et al (2005) Effects of levosimendan on systemic and regional hemodynamics in septic myocardial depression. Intensive Care Med 31:638–644. doi: 10.1007/s00134-005-2619-z
15. Mebazaa A, Nieminen MS, Packer M et al (2007) Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE randomized trial. JAMA 297:1883–1891. doi: 10.1001/jama.297.17.1883