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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	e and future inotropic agents				
	Dobutamine	Adrenaline	Milrinone	Levosimendan	Omecamtiv
Substance class Mechanism of inotropic effect	Catecholamines Beta-adrenergic receptor- mediated increase of cAMP synthesis	Catecholamines Beta-adrenergic receptors- mediated increase of cAMP synthesis	PDE III inhibitor Decreased breakdown of cAMP through inhibition of PDE III	Calcium sensitizer Enhanced troponin C sensitivity to intracellular calcium	Myosin activator Increased actin-myosin cross-bridging by direct stimulation of cardiac
Half-lif <mark>e</mark>	2–3 min	2 min	2 <mark>h</mark>	1 h, metabolite (OR-1896)	10 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 <u>directly stimulates the actin-myosin cross-bridging</u>, 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/m² 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, sepsisinduced 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.

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Dear Editor,

We read with interest the excellent concept of understanding the differences among inotropes by Dr. Arrigo and Mebazaa [1], but what are missing are the goals of inotropic therapy in patients with cardiogenic and/or septic shock and the differences between the substances to reach these goals. This is important, since it was shown that dobutamine, despite its positive effect on increasing cardiac output, is not associated with improved mortality in patients with heart failure, and there is even a suggestion of increased mortality associated with its use [2]. The

factors leading to this negative effect also restore important organ functions are multiple: one important issue could be a missing or even a negative effect on liver function induced by dobutamin in these patients. Cardiogenic shock is associated with decreased liver blood flow and function, and increased cytokine production [3]. The importance of the gut-liver axis in these situations is underlined by the fact that cytokines are predominantly produced by the Kupffer cells. In this situation, dobutamin does not improve liver blood flow. Indeed, in one study of dobutamine therapy for patients with cardiogenic shock, even a trend towards decreased liver blood blow was observed [4]. In contrast, levosimedan has been shown to increase blood flow to the small intestine and liver in anesthetized dogs. In patients with advanced decompensated heart failure [5] and septic shock, levosimedan increased liver blood flow and decreased pro-inflammatory cytokine levels, which could not be seen in patients treated with dobutamine. The increase in liver blood flow and liver function and decrease in cytokines during and after a levosimedan infusion was confirmed recently in patients with acute or chronic heart failure. Therefore, we think an "ideal" inotropic agent should not only improve cardiac function but



like the the gut-liver axis.

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