Inotropes

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Abstract

Inotropes increase the force of contraction of cardiac muscle and thereby increase cardiac output. In general, they are used to prevent anaerobic metabolism by improving oxygen delivery to the tissues. Inotropic agents have varying pharmacological profiles; drug selection according to the clinical circumstance enables benefits to be maximized while minimizing side effects. Most inotropes act to increase intracellular calcium levels. Adrenoceptor agonists (e.g. epinephrine) achieve this by activating adenylate cyclase and increasing cyclic adenosine monophosphate (cAMP) levels and protein kinase activity, which potentiates the opening of voltage-gated calcium channels and increases the amount of calcium released from the sarcoplasmic reticulum. Phosphodiesterase inhibitors (e.g. milrinone) block the degradation of cAMP, thereby increasing protein kinase activity and calcium levels. Raised intracellular calcium is, however, associated with arrhythmias and cell death, leading to the development of newer agents that act by different mechanisms. Levosimendan improves the sensitivity of the contractile apparatus to calcium, thereby increasing inotropy. Epinephrine remains the drug of choice in emergencies (cardiac arrest, anaphylaxis). Inotropes are commonly administered by controlled infusion in the critical care environment, to allow close monitoring and careful titration. The combined use of several inotropes in lower doses may confer a benefit over single agents used at high doses.

Keywords Cardiac output; dobutamine; dopamine; dopexamine; enoximone; epinephrine; inotropy; isoprenaline; levosimendan; lusiotropy; milrinone; norepinephrine

Royal College of Anaesthetists CPD Matrix: 1A02 2C03

Learning objectives

After reading this article, you should be able to:

- explain the term 'lusiotropy'
- describe the haemodynamic effects of epinephrine
- have a brief understanding of the future of inotropes

Introduction

Inotropic agents are drugs that affect the force of contraction of myocardial muscles and their effects can either be positive or negative. In clinical practice, however, inotropes are synonymous with positive inotropes. They are the mainstay in the treatment of important cardiovascular syndromes which severely compromise cardiac output and thus oxygen delivery, and are routinely used in anaesthesia, intensive care and coronary care. However as recent evidence shows, their use can have unintended consequences leading to toxicity and harm. They can precipitate malignant arrhythmias, damage to arterial walls leading to focal myocardial contraction band necrosis and directly stimulate myocyte apoptosis. As such it is important to have a clear understanding of their pharmacology to allow for the precise selection of the appropriate agent for the clinical situation at hand in order to achieve a targeted clinical outcome. We will first review the physiology of cardiac output and myocyte contractility prior to an in-depth review of the pharmacology of the different inotropic agents. Finally, we will review what is on the horizon in the development of novel inotropic agents.

Cardiac output

The heart acts as the pump which delivers oxygen to all cells in the body to fuel aerobic metabolism. Cardiac output along with the oxygen content of arterial blood (both bound to haemoglobin and dissolved) the essential components of oxygen delivery as shown by the oxygen delivery equation ($Do_2 = CO \times Cao_2$). Cardiac output is the product of heart rate and ventricular stroke volume ($CO = HR \times SV$). It can be manipulated through changes in preload (Frank–Starling mechanism), contractility and afterload. The cellular mechanism by which cardiac myocytes shorten and produce the force needed to propel blood from the ventricle, is discussed in *Anaesthesia & Intensive Care Medicine* 2012; **13(8)**: 388–390.

Inotropic agents act to increase contractility, thereby increasing cardiac output and oxygen delivery to tissues. The healthy heart has considerable reserve and cardiac output can increase by sevenfold to match oxygen delivery requirements during intense exercise. This is achieved through increases in preload (via increasing venous return), heart rate (chronotropicity, via sympathetic system activation) and contractility (inotropy, via sympathetic system activation).

The diastolic function of the heart is also crucial to its function, with diastolic dysfunction recognized as an independent cause of heart failure. Optimal ventricular filling is dependent on efficient myocardial relaxation (lusiotropy) and ventricular chamber compliance. Lusiotropy is an active process requiring energy and can be upregulated by β-adrenergic stimulation.

Clinical use of inotrope

Inotropes are used to restore cardiac output and thereby tissue perfusion and oxygenation when haemodynamic insufficiency limits oxygen supply to tissues (Figure 1). As with any intervention it should never be commenced blindly and a careful assessment of the underlying pathology leading to shock should be undertaken. This will allow for the selection of the most appropriate inotrope for the clinical circumstance in order to maximize the benefit and minimize harmful side effects.

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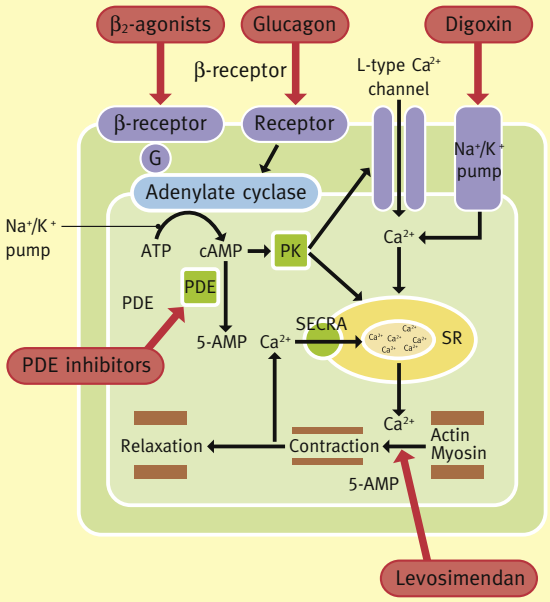
Summary of myocyte physiology and sites of inotrope action



ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; G, G protein; PDE, phosphodiesterase; PK, protein kinase; SERCA, sarco/endoplasmic reticulum Ca^{2+} ATPase; SR, sarcoplasmic reticulum.

Figure 1

Classification of inotropic agents

Mechanism of action	Cellular mechanism	Example
↑ $[Ca^{2+}]_{intracellular}$	Calcium salts	Calcium chloride
	↑ $[cAMP]_{intracellular}$	β_1 Agonist (epinephrine, dobutamine, dopamine)
		Phosphodiesterase inhibitor (milrinone, enoximone)
		Glucagon
	Na^+/K^+ ATPase inhibition	Digoxin
	Na^+/K^+ ATPase inhibition with SERCA activation	Istaroxime
Calcium sensitization	↑ Troponin C affinity for Ca^{2+}	Levosimendan
Cardiac myosin activators	Accelerate rate of actin-dependent phosphate release of the actin–myosin cross-bridge	Omecamtiv mercarbil
SERCA activation	Reduce sarcoplasmic reticulum re-uptake of calcium and abnormal leak of calcium into the SR	Nitroxyl
Ryanodine receptor stabilization	Reduce abnormal calcium leak from the SR	S44121

ATPase, adenosine triphosphatase; cAMP, cyclic adenosine monophosphate; SERCA, sarco/endoplasmic reticulum Ca^{2+} ATPase; SR, sarcoplasmic reticulum.

Table 1

Inotropes should be administered and titrated in a critical care environment with cardiovascular and haemodynamic monitoring given the potency and potential side effects. This should include continuous electrocardiogram (ECG) and invasive blood pressure monitoring as well as oxygen saturation, urine output and regular neurological assessments. Regular metabolic assessments of perfusions via arterial blood gas sampling can aid inotrope selection and titration. Filling status is important and can be estimated by central venous pressure from a central venous catheter, which also allows for administration of inotropic agents. More advanced monitoring of haemodynamics may be employed in patients who are unstable and on multiple inotropic agents. This may include monitoring of cardiac output, systemic and pulmonary vascular resistances and mixed venous oxygenation via the pulmonary artery flotation catheter or pulse contour analysis techniques such as the PiCCO.[1] Finally echocardiography can be employed to diagnose the cause of shock and to assess the effectiveness of inotropic therapy.[2]

Classification of inotrope

When examining the cellular mechanism of force production by the cardiac myocytes it is clear that inotropy is dependent on three factors: (1) the concentration of intracellular calcium, (2) the sensitivity of the contractile proteins to the intracellular calcium present and (3) the duration of actin–myosin cross-bridge binding. Hence, the classification of inotropes can be based on these dependent variables (Table 1):

- increase in concentration of intracellular calcium:
  - calcium salts
  - increase in cyclic adenosine monophosphate (cAMP) concentrations:
    - β_1 agonists
    - phosphodiesterase inhibitors
    - glucagon
  - Na^+/K^+ ATPase inhibitors: digoxin
  - new approaches to rebalance intracellular calcium concentration:
    - SERCA activation
    - Ryoanodine receptor stabilization
- increase in affinity of troponin C for Ca^{2+}: levosimendin
- increase in response of myofibrillar proteins to a given concentration of Ca^{2+}: omecamtiv mecarbil.

The beneficial effects of the most widely used inotropic agents in critical care are derived from their ability to increase intracellular calcium which coincidentally is also directly responsible for the adverse effects including ischaemia, arrhythmia, ventricular ectopy, band necrosis and myocyte apoptosis. As a result, recent inotropic drug development have been aimed at increasing contractile protein function without the need to increase