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Positive Inotropic Agents in Myocardial Ischemia–Reperfusion Injury

A Benefit/Risk Analysis

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POSITIVE inotropic agents are widely used in the perioperative setting, particularly in patients undergoing cardiac and major vascular surgeries. While they can be utilized to provide life sustaining support in circumstances of severe right and/or left cardiac ventricular failure and to improve both clinical symptoms experienced by patients and systemic end-organ perfusion, overuse of inotropes should be avoided in order to avert potential harm that can be incurred from deleterious influences on myocyte oxygen consumption which can lead to cardiac arrhythmias and myocyte death.[1] Besides, their benefits on medium- and long-term survival, especially in the setting of myocardial ischemia and reperfusion (acute coronary syndrome, revascularization by coronary angioplasty, perioperative acute myocardial infarction, and cardiac surgery with or without cardiopulmonary bypass), have never been validated.[2] Finally, there is a great variability in the use of inotropes, depending on the centers and the practitioners.[3] In this review, the mechanisms and traditional uses of positive inotropic agents will be discussed and we will develop the potential risk and benefits of positive inotropes and the crucial role of their rationale use in the setting of myocardial ischemia–reperfusion injury.

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Applied Pharmacology of Positive Inotropic Agents

Characteristics of an ideal positive inotrope are outlined in table 1. To date, none of the available agents satisfies all these criteria and there is no current evident data coming from evidence-based medicine to recommend the choice of a positive inotropic drug rather than another for daily practice. The positive inotropic agents can be listed according to their cellular signaling pathways (fig. 1). We distinguish the catecholamines, the type III phosphodiesterase inhibitors (PDEIs III), the cardiac glycosides, and the calcium sensitizing agents (levosimendan).

1. The catecholamines (α/β adrenoceptors)

The catecholamines are the most frequently used positive inotropic agents over the perioperative period. With an elimination half-life of just a few minutes, their on/off properties are quite appreciated at the bedside. We can in broad outline divide them into inoconstricting catecholamines (with positive inotropic and vasoconstrictive properties) and inodilative catecholamines (with positive inotropic and vasodilative properties; table 2). All catecholamines have some positive inotropic and chronotropic effects that vary by orders of magnitude depending upon the agent used (table 2).[4] The catecholamines exert their positive inotropic effect mainly *via* the stimulation of the cardiac myocyte β1-adrenoceptor (fig. 1). However, their β2-adrenergic (isoproterenol and dopexamine) and α1-adrenergic (epinephrine and norepinephrine) agonist effects at the level of the cardiac myocyte also provide inotropic support useful in clinical situations where the β1-adrenoceptor is down-regulated, as in congestive chronic heart failure.[5] Besides, the β2-adrenoceptors located on the blood vessels and smooth muscles of the bronchi result in vasodilation that yields cardiac afterload reduction and bronchodilation. As well, α1-adrenoceptors

Table 1. Theoretical Clinical Characteristics of the Ideal Positive Inotropic Agent: None of the Available Agents in Practice Satisfies All the Criteria

Easy titration for rapid on/off effect
Myocardial oxygen supply/demand balance
Steady effect in time (no tachyphylaxis)
Direct positive inotropic effect
β-independent positive inotropic stimulation*
Few or no arrythmogenic
No increase in intracellular calcium overload
Maintenance of the coronary perfusion pressure
Beneficial effects on regional vascular beds (renal, splanchnic)
Reasonable benefit/risk balance

* That kind of inotropic stimulation avoids tachyphylaxis and seems particularly interesting in clinical situations in which the β1-adrenergic receptor is down-regulated.

predominate on the vasculature, resulting in vasoconstriction. The clinical situations (congestive chronic heart failure and cardiac transplant) with depletion in the neurotransmitter norepinephrine can compromise the ability of indirect-acting amines (dopamine and dopexamine) to provide effective inotropic support.[6] Indirect effects of dopamine include inhibition of norepinephrine reuptake at the nerve terminal, release of norepinephrine at the nerve terminal, and metabolism to form norepinephrine. Dopexamine is a synthetic β2-adrenoceptor agonist that exerts positive inotropic and vasodilative effects. It also acts as a moderate dopaminergic agonist (table 2).

2. The PDEIs III

The PDEIs III provide myocardial inotropy *via* a mechanism different from those of catecholamines, as they act by preventing the breakdown of cyclic adenosine monophosphate, prolonging its effectiveness and increasing its physiologic response (fig. 1). Exerting their positive inotropic stimulation independently from the β1-adrenoceptor, PDEIs III seem potentially useful in patients with chronic heart failure where they are often used coupled with catecholamines such as epinephrine for synergistic improvement in myocardial contractility. In addition to positive inotropic effects, PDEIs III cause vasodilation and reduction in cardiac

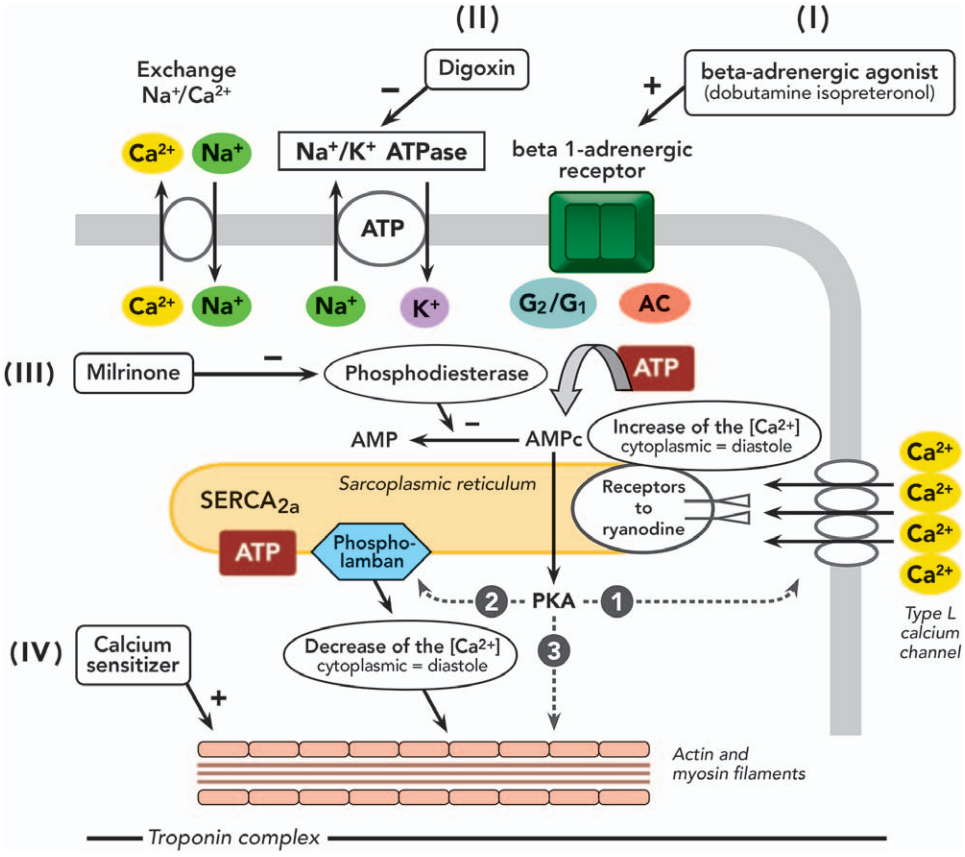

Fig. 1. Cardiomyocyte cellular mechanisms of action of positive inotropic agents. (I): the β-adrenergic agonists (dobutamine and main catecholamines); (II): the cardiac glycosides (digoxin); (III): the type III phosphodiesterase inhibitors (milrinone); (IV): the calcium sensitizing agents (levosimendan). AC = adenylate cyclase; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; G1 = stimulating G protein; G2 = inhibitory G protein; PKA = protein kinase A; SERCA = sarcoplasmic reticulum calcium pump. Modified, with permission, from Fourati M, Methamen M, Mebazaa A: Choix pratique et raisonné d'un agent inotrope positif en chirurgie cardiaque. Anesthésie-réanimation en chirurgie cardiaque: Nouveaux concepts et perspectives. Edited by Fellahi JL. Paris, Arnette, 2006, pp 181–90.

Table 2. Classification of Catecholamines According to Their Effects on Main Types of Adrenergic (α1, β1, and β2) and Dopaminergic (DA1) Receptors: We Distinguish Inoconstricting Catecholamines from Inodilative Catecholamines

	Receptors			
Agonists	α1	β1	β2	DA1
Inoconstrictors				
Norepinephrine	+++	+	0	0
Epinephrine	+++	+++	++	0
Dopamine*	++	++	+	++
Inodilators				
Dobutamine	+	+++	++	0
Dopexamine	0	+	+++	+
Isoproterenol	0	+++	+++	0

* The affinity of dopamine for different receptors is classically dose dependent: the dopaminergic effect is predominant from 2 to 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$; the β-agonist effect is predominant from 5 to 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$; and the α-agonist effect is predominant at >10 $\mu g \cdot kg^{-1} \cdot min^{-1}$. A great interindividual variability is, however, observed in clinical practice.

filling pressures, and pulmonary and systemic vascular resistance. Three PDEIs III have been used clinically: inamrinone, milrinone, and enoximone. The pharmacokinetics of the PDEIs III is such that they are not easily titratable for fast on/off use (*e.g.*, milrinone has a half-life of almost 2 h).

3. The cardiac glycosides

Cardiac glycosides (digoxin) bind to the extracellular surface of the α subunit of myocardial Na-K-ATPase and inactivate this enzyme system (fig. 1). The potential benefit of digoxin therapy in patients with chronic heart failure results from both an overall increase in myocardial contractility and a decrease in ventricular pressures. Digoxin has however a narrow therapeutic index and provides only a modest positive inotropic support. Moreover, one of the most potentially life-threatening side effects of cardiac glycosides is ventricular arrhythmia. For these reasons, discontinuing digoxin during the perioperative period should be considered.

4. Levosimendan

Levosimendan acts as an inodilator. It enhances myocardial contractility by binding to the cardiac troponin C with a high affinity and stabilizing the Ca^{2+}-bound conformation of this regulatory protein.[7] Thus, levosimendan provides inotropic support without increasing intracellular Ca^{2+} concentrations which, in context with neutral effects on myocardial oxygen demand and heart rhythm, should be of benefit compared with catecholamines or PDEIs III. Levosimendan also produces vasodilation in several vasculatures, including coronary, pulmonary, renal, splanchnic, cerebral, and systemic arteries and veins.[7] Finally, levosimendan has protective myocardial properties *via* the stimulation of adenosine triphosphate-dependant potassium channels[7] which could be particularly beneficial in the setting of ischemia–reperfusion injury. Levosimendan has been extensively investigated in experimental studies and that is also increasingly the subject of clinical trials in the setting of acute decompensation of chronic heart failure[8,9] or ischemia–reperfusion[10] and also in the perioperative setting.[11]

The Rationale to Use Positive Inotropic Agents in the Perioperative Period

Because the low-cardiac output syndrome contributes to postoperative morbidity and mortality, and increases length of hospital stay and costs, it is desirable to minimize its occurrence or attenuate its severity by using inotropic support to achieve an adequate hemodynamic status and improve systemic end-organ perfusion. In cardiac surgery, numerous risk factors associated with the prescription of positive inotropic agents over the perioperative period have been described, including factors related to the patient (advanced age, poor preoperative left or right ventricular function, unstable coronary syndrome, significant arrhythmias, severe valvular diseases, diabetes mellitus, and renal insufficiency) and factors related to the surgery (emergency, reoperation, combined surgery, prolonged cardiopulmonary bypass, and cardiac transplantation). However, the reasons why one or several positive inotropic agents are used in practice for a given patient are less well-defined, depending on the considered centers and for a given center depending also on the practitioners working there. In the United States[12] as in Europe,[13] the personal habits of the anesthesiologist in charge of the patient represents a daily decisive individual factor to potentially use positive inotropic agents. In France,[3] an observational study including 1,368 patients recruited from 40 cardiac surgery centers reported an overall rate of 38% for catecholamine use with great intercenter variations, going from 10% of patients to a systematic administration. In this last study, 91% of all the prescription of positive inotropic agents were performed on a case-by-case basis, without any written department protocol or fixed decisional algorithm. Despite the fact that advanced hemodynamic monitoring has been clearly identified as a decisive tool to support the use of inotropes in cardiac surgery,[14] the occurrence of a single hypotension was the main reason to use one or several catecholamines in more than 80% of cases.[3] Globally, these results show the important heterogeneity of practical use of positive inotropic drugs for a given surgery and may suggest a possible hazardous or inappropriate prescription for some surgical patients. A possible interpretation of this statement is the commonly accepted concept that if "a few micrograms of catecholamines are not good, they will not anyway be bad," a concept maintained by the absence of a consensus regarding the management of the low-output cardiac syndrome[15] and scarce data coming from evidence-based medicine on the potential risks related to the use of catecholamines or the PDEIs III in clinical situations of perioperative myocardial ischemia–reperfusion injury.

Potential Detrimental Effects of Positive Inotropic Agents in the Setting of Acute Myocardial Ischemia–Reperfusion Injury

There are arguments against prophylactic or unnecessary perioperative use of positive inotropic agents in cardiac surgery and probably in any clinical situation with risk of myocardial acute ischemia–reperfusion injury. These arguments include the worsening of the intracellular calcium overload in cardiomyocyte level, the increase in the myocardial energy imbalance, and the relatively low prevalence in practice of the acute postoperative myocardial dysfunction.

1. Calcium overload

The concentration in intracellular free calcium ($[Ca^{2+}]i$) is multiplied by a factor going from 10 to 100 from the first minutes of the ischemic period to reach a paroxysm at the reperfusion initial phase.[16] This massive intracellular calcium overload is directly or indirectly involved in all the clinical manifestations of the ischemia–reperfusion syndrome in humans. Actually, it is supposed to participate directly in the appearance of malignant ventricular arrhythmias during reperfusion and, through a vasoconstriction, would contribute to the worsening of the coronary endothelial dysfunction. Finally, through a decrease in the myofilament's sensitivity to calcium, it would also participate in the phenomenon of postischemic myocardial stunning. The main positive inotropic agents used in clinical practice induce a major increase in the intracellular cyclic adenosine monophosphate rate (either increasing the production for catecholamines, or decreasing the degradation for PDEIs III), which itself leads to a transitory increase in the $[Ca^{2+}]i$ responsible for the researched positive inotropic effect, but at the cost of a modification of the myocardial energy balance which speeds up in the end the cell death. Furthermore, increased concentrations of cyclic adenosine monophosphate and the subsequent changes in $[Ca^{2+}]i$ turnover are cardiotoxic and enhance electrophysiologic mechanisms that result in rhythm disturbances.[17] In contrast, the mechanism of action of levosimendan may be the reason for the parallel enhancement of myocardial contractility and improvement of diastolic function without promoting arrhythmogenesis in experimental and clinical studies.[7]

2. The myocardial oxygen supply/demand imbalance

Any situation of myocardial ischemia–reperfusion is responsible for a constant energetic imbalance of the myocardium. The use of positive inotropic agents in this context exposes necessarily to additional worsening risks of this imbalance and to risks of first appearance of additional acute myocardial ischemic lesions, responsible in turn for a modification of the left and/or right ventricular overall myocardial performance. Actually, the increase in the inotropism related to the catecholamines or the PDEIs III stimulation is necessarily done at the cost of a significant increase in the myocardial consumption in oxygen. The inoconstrictor agents, responsible for a simultaneous increase of the systolic constraint and thus of the left ventricular afterload, are therefore especially expensive regarding the energetic level, justifying the first choice of an inodilator when possible.[18] Finally, acceleration of the heart rate may have a detrimental effect on the myocardial energy balance, unfavorably weighing on the consumption and on the myocardial inputs in oxygen. The consequences of this imbalance in terms of myocardial functional recovery are far from being insignificant. The use of a high dose of dopamine for 30 min to normalize the segmental contractility during a transitory coronary occlusion was experimentally responsible for a significant delay of the myocardial functional recovery 24 h after the acute ischemic episode compared to a control group of animals that did not receive dopamine.[19] Even if all the catecholamines are not identical in this area, the inoconstrictor agents being probably more deleterious than the inodilative agents,[20] it is essential to underline the potentially dangerous nature of an increase in the tissue extraction in oxygen within an organ, the heart, whose extraction is already quasi-maximal in basal conditions. Again, the pharmacologic properties of levosimendan could explain why myocardial contractility is increased without promoting alterations of myocardial oxygen demand in experimental and clinical studies.[7]

3. Incidence of perioperative myocardial dysfunction

Three main types of macro circulatory abnormalities can lead to acute circulatory failure during the perioperative period: hypovolemia, vascular dysfunction, and myocardial dysfunction. Hypovolemia is statistically the most frequent and occurred in approximately 50% of cases. All the complexity lies in the right assessment of the blood volume and above all of the response to the vascular filling at the bedside.[21] The vascular dysfunction (10–40% of cases) is often transitory and can only be recognized after correction of a potential hypovolemia and elimination of a myocardial dysfunction on echocardiography. Occurring after cardiopulmonary bypass and/or prolonged myocardial ischemia, hypotension secondary to vasodilation should be treated first by the use of selective α1-agonist vasopressors with transition to an inoconstrictor agent such as the norepinephrine if there is also a concurrent problem with myocardial contractility. The postoperative acute myocardial dysfunction is much rarer, occurring in nearly 20% of cases. Multifactorial, partly linked to the postischemic myocardial stunning, it sometimes comes from a legitimate prescription of positive inotropic agent. The prescription must then be reasonable and favor the less deleterious positive inotropic agent, with the lowest possible dose, for the shortest period, and at the best benefit/risk balance. European recommendations for the management of a perioperative acute cardiac failure in cardiac surgery have recently been published.[18] They suggest three options either alone or combined: low to moderate doses of dobutamine and/or epinephrine, milrinone, and levosimendan. Norepinephrine can be associated in case of simultaneous vascular dysfunction.[18] When there is no definite criterion likely to impose the choice of the positive

inotropic agent, the medical decision relies in practice on several related clinical arguments and on the practitioner's personal experience. Using echocardiography to allow real-time assessment of intracardiac volumes, valvular insufficiencies, and contractility of the right and left ventricles can be an invaluable aid in appropriate titration of positive inotropes.[14] As no consensus exists regarding the treatment of low-cardiac output syndrome,[22] alternatives or adjuncts to positive inotropic agents such as intraaortic balloon pump, ventricular assist devices, and resynchronization therapy[23] can also be proposed to achieve an adequate hemodynamic status.

Risks Associated with the Inappropriate Use of Positive Inotropic Agents in the Setting of Acute Myocardial Ischemia–Reperfusion Injury: The Evidence-based Medicine

The cardiologists were the first to underline the risks and adverse effects on a short and medium term related to the use of positive inotropic agents in decompensated chronic heart failure. The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study showed the absence of benefits related to the PDEIs III use on 60-day mortality.[24] Besides, the hemodynamic adverse effects (hypotension and arrhythmias) were significantly more frequent in the group treated with milrinone. This last statement was even more obvious in the subgroup of patients presenting an advanced ischemic cardiopathy,[25] underlining the special risk related to the use of positive inotropic agents in patients presenting myocardial ischemia. Likewise, a retrospective analysis conducted from the national Acute Decompensated Heart Failure National Registry (ADHERE) showed an inhospital increased mortality in the group of patients treated with a positive inotropic agent (dobutamine or milrinone) compared to those receiving either a nitrous derivative, or nesiritide.[26] The risk of inhospital increased mortality when catecholamines are given to patients with a decompensated heart failure has been recently confirmed,[27] and levosimendan did not show any benefit compared to the dobutamine on survival long after an acute episode of chronic heart failure decompensation.[9] Thus, in spite of an undeniable transitory improvement of the left and right ventricular contractility and of the clinical symptoms presented by patients with decompensated chronic heart failure, the use of positive inotropic agents goes with an increase in the hemodynamic adverse effects and does not provide any improvement of the survival on a short and medium term.

In the perioperative setting, a recent systematic review of the literature was unable to find any data relating to the effect of main catecholamines and PDEIs III on major clinical outcomes or survival in cardiac surgery patients.[15] The authors concluded that multicenter randomized controlled trials focusing on clinical rather than physiological outcomes were needed. In cardiac surgery, we showed that the use of dobutamine was associated with a serious inhospital cardiac increased morbidity (malignant ventricular arrhythmias and myocardial infarction) without worsening of the overall mortality.[28] This last study, consistent with the results obtained in decompensated chronic heart failure, provides a strong argument against the liberal use of catecholamines in cardiac surgery and encourages to consider it only when the immediate survival of the patient is at stake.[29] Recent meta-analyses suggested that milrinone might increase mortality in patients undergoing cardiac surgery,[30] and that levosimendan might reduce hospital stay and improve short-term survival in cardiac surgery and cardiology settings of adult patients.[11] Fundamental studies have identified a genetic polymorphism in the expression of the β-adrenergic receptor which could be associated with a more frequent need in β-adrenergic agonists after a coronary revascularization surgery.[31]

Future of Inotropic Agents

Current inotropic drugs have consistently failed to show beneficial effects beyond short-term hemodynamic improvement in patients with acute heart failure.[2] Therefore, new agents that may increase the benefit and decrease the risks associated with current inotropes are being developed. These agents target novel mechanisms. Istaroxime is a nonglycoside inhibitor of the Na-K-ATPase with additional stimulatory effects on the sarcoplasmic reticulum calcium pump and has shown lusitropic and inotropic properties in experimental and early clinical studies.[2,32] Cardiac myosin activators are recently discovered small molecules that stimulate directly the activity of cardiac myosin motor protein, resulting in improvement of cardiac contractility without changes in $[Ca^{2+}]i$.[32] Gene therapy approaches have been successfully employed to increase myocardial sarcoplasmic reticulum calcium pump.[2] Nitroxyl donors, ryanodine stabilizers, and energetic modulators may also represent promising means to improve contractile performance of the heart with a favorable safety profile.

Conclusions

Surgical patients with low-cardiac output syndrome may require positive inotropic agents in order to improve their immediate odds of survival. However, these drugs should be used only as needed to maintain adequate end-organ perfusion. The potential serious adverse effects, especially in clinical situations of myocardial ischemia–reperfusion injury, suggest that risk benefits should be carefully contemplated by the practitioners and that advanced hemodynamic monitoring should be systematically used. Waiting for large multicenter studies to assess long-term impact and different combinations of inotropes, and pending the clinical confirmation of the potential interest of new positive inotropic agents, anesthesiologists should focus on practice standardization including advanced hemodynamic monitoring, improvement of the quality of care (risk–benefit ratio), and improvement of the pharmacological and economic logistic (cost–efficiency ratio).

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