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Inotropes and Vasopressors Use in Critical Care and Perioperative Medicine: Evidence-Based Approach (Review)

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Применение инотропных препаратов и вазопрессоров в реаниматологии и периоперационной медицине: доказательный подход (обзор)

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Summary

Inotropes and vasopressors are frequently required in critically ill patients and in patients undergoing major surgery. Several molecules are currently available, including catecholamines, phosphodiesterase-3 inhibitors, vasopressin and its analogues, and calcium sensitizers.

We will review current evidence on inotropes use in perioperative and critically ill patients, with focus on most recent randomized controlled trials (RCTs).

Despite being widely used in anesthesia and intensive care, evidences on safety and efficacy of inotropes are scarce. Data from observational studies suggest that inotropes administration may increase mortality in cardiac surgery, acute heart failure, and cardiogenic shock patients. However, randomized controlled trials did not confirm these findings in acute care settings.

Epinephrine has been associated with increased mortality especially in cardiogenic shock, but randomized trials failed to show evidence of increased mortality associated with epinephrine use. Norepinephrine has been traditionally considered contraindicated in patients with ventricular dysfunction, but recent trials suggested hemodynamic effects similar to epinephrine in patients with cardiogenic shock. Dopamine has no additional advantages over norepinephrine and increases the risk of tachyarrhythmias and may increase mortality in cardiogenic shock. Phosphodiesterase-3 (PDE-3) inhibitors are equivalent to catecholamines in terms of major outcomes. Levosimendan is the most investigated inotrope of the last 30 years, but despite promising early studies, high-quality multicenter RCTs repeatedly failed to show any superiority over available agents. There is no high-quality RCT clearly demonstrating superiority of one agent over another. In summary, current evidence suggest that the choice of inotrope is unlikely to affect outcome, as long as the target hemodynamic goals are achieved.

Finally, in recent years, mechanical circulatory support (MCS) has become increasingly popular. Thanks to improvement in technology, the safety and biocompatibility of devices are constantly growing.

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MCS devices have theoretical advantages over inotropes, but their use is limited by costs, availability, and invasiveness.

Conclusion. Future studies should investigate safety, efficacy, and cost-effectiveness of primary MCS versus primary inotropes in patients with acute cardiovascular failure.

Keywords: hemodynamic management; inotropes; vasopressors; catecholamines; shock; intensive care; mortality

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Introduction

It is well recognized that low cardiac output (CO) state is associated with an increased risk of organ dysfunction, hospital stay, and mortality, both in critical illness and post-operative settings [1–5]. More in general, the inability of the circulatory system to match oxygen demand is considered the main pathophysiological cause underlying the development of multi-organ failure and death [6].

Cardiac output is a key determinant of oxygen delivery. When heart function is incapable of providing enough CO to support tissues metabolic demands, inotropes can be administered with the goal of improving cardiac contractility and, therefore, restore and maintain an adequate oxygen delivery [7, 8].

As a consequence, inotropes are well-known medications to every physician caring for patients with any kind of cardiovascular dysfunction. These typically includes patients with acute and chronic heart failure, patients undergoing cardiac surgery, but also patients with septic shock, major trauma, or undergoing high-risk non-cardiac surgery. In general, every critically ill patient may require some degree of inotropic support.

Inotropic drugs have been administered for decades to patients with heart failure, and, as many other intervention (e. g. blood products transfusion, intra-aortic balloon pump), entered in routine clinical practice well before development of the «Evidence-Based Medicine» concept, and their safety and efficacy have never been formally tested.

Aim of this review is to summarize current evidence regarding use of inotropes and vasopressors in critically ill patients.

Hemodynamic and Side Effects of Inotropic Agents

Every available inotropic agent increases cardiac contractility and CO to a variable degree. Effect on vascular tone is variable, with some agents being also vasoconstrictors («inoconstrictors» or «inopressors») and other vasodilators («inodilators»). As a result, the net effect on mean arterial pressure (MAP) is variable, and, as it depends also on volume status of the patient, may not be easy to predict. Pure vasoconstrictors generally increase mean arterial pressure, while the effect on CO is variable and dependent from baseline cardiac function and indirect effects on heart rate, although they do generally reduce CO while increasing MAP [9, 10]. A list of the most frequently used agents and their hemodynamic effects is presented in Table 1 [8, 11–16].

Despite the proven positive hemodynamic effects, inotropes are not free from side effects. The most frequently described are tachycardia, ventricular and supraventricular arrhythmias, and (with the possible exception of levosimendan [17,18]) increase in myocardial oxygen consumption [7, 19, 20]. In addition, inodilator agents may also cause severe hypotension [18, 19], while inoconstrictors may cause limb and mesenteric ischemia [21].

Catecholamines, the most frequently used inotropic agents, also have a wide range of effects on respiratory, gastrointestinal, endocrine, immunological and coagulation system that could result detrimental when adrenergic stimulation becomes excessive [22–25]. Increase in cardiomyocytes apoptosis may be particularly important in patients with a limited cardiovascular reserve [26–28] and cardiac side effects have been described in almost half of patients receiving catecholamine therapy [20].

Current Evidence by Clinical Settings

Between the end of the 80s and the early 90s, several large randomized trials demonstrated an increase in mortality in patients with chronic, stable heart failure treated with daily administration of inotropes, regardless of molecule tested [29–31] and with the exception of oral digoxin, which showed a neutral effect on mortality [32]. Since then, it is generally accepted that, in patients in a stable clinical condition, side effects of inotropes outweigh the positive hemodynamic effect of these drugs.

More recently, several authors have raised concerns regarding safety of inotropes also in «acute» clinical settings.

Several observational trials and data from registries have found an association between inotropes administration and mortality in patients presenting with acute heart failure [33–39]. In addition, some meta-analyses also highlighted a trend towards increased mortality when catecholamines are administered in patients with heart failure [40, 41]. In more recent years, observational studies have suggested reduced survival associated with inotropes administration also in the settings of cardiac surgery [42–44] and septic shock [45]. Of note, other observational trials did not found a similar association [46].

Despite evidences from observational trials, there is currently no randomized clinical trial demonstrating that inotropes administration increase mor-

Table 1. Summary of hemodynamic effects of commonly used inotropes/vasopressors.
Modified from Jentzer et al.

Drug	Pharmacology	Main teoretical hemodynamical effects				
		CO/CI	SVR	PCWP	MAP	HR
Dopamine (>4 мкг/кг/мин)	β_1-agonist ≈α-agonist > β_2-agonist	↑	↑	↑	↑	↑↑
Dobutamine	β_1-agonist > β2-agonist >> α-agonist	↑↑	↔↓	↔↓	↑↔↓	↑
Norepinephrine	α-agonist > β_1-agonist > > β_2-agonist	↑↓	↑↑	↑	↑↑	↑↔
Epinephrine	β_1-agonist ⩾ α-agonist ⩾ β_2-agonist	↑↑	↑	↑	↑↑	↑↑
Milrinone/ Enoximone	PDE-3 inhibitor	↑↑	↓↓	↓↓	↓↔	↑↔
Levosimendan	Calcium-sensitizer + PDE-3 inhibitor	↑↑	↓↓	↓↓	↓↔	↑↔
Digoxin	Na^+/Ca^+ ATPase inhibitor	↔↑	↔	↔↓	↔↑	↓
Vasopressin	$V_1 + V_2$ vasopressin receptor agonist	↓	↑↑	↑	↑↑	↔↓
Terlipressin	Selective, long-acting V_1-vasopressin receptor agonist	↓	↑↑	↑	↑↑	↔↓
Angiotensin II	Angiotensin receptor agonist	↓	↑↑	↑	↑↑	↔↓

Note. CI — cardiac index; CO — cardiac output; HR — heart rate; MAP — mean arterial pressure; PCWP — pulmonary capillary wedge pressure; PDE-3 — phosphodiesterase-3; SVR — systemic vascular resistances.

tality in settings other than chronic stable heart failure [47]. On the contrary, inotropes may actually improve survival in certain clinical settings [47].

Cardiac Surgery

In cardiac surgery, patients frequently receive inotropes. In several series, more than 50% of patients required some degree of inotropic support [48], although use of inotropes remains highly variable [46, 49, 50]. Difficult weaning from cardiopulmonary bypass and post-operative low cardiac output syndrome (LCOS) are the most frequent indication for inotropes administration [4, 51, 52]. Cardiac function frequently declines in the first hours following cardiac surgery [53, 54], and it's a common experience for the cardiac anesthesiologist or intensivist to treat patients with inotropes for few hours to restore adequate organ function. Rapid clinical deterioration is also frequently seen following inappropriate inotrope discontinuation. Several trials comparing inotropes against each other and against non-inotropic drugs have been published. Unfortunately, studies are small and not powered enough to adequately assess clinically relevant endpoint [11, 47], with the notable exception of levosimendan, the only agent investigated in several multicenter RCTs [55–58]. Definitive evidence strong enough for high-grade recommendations is lacking, even though it is almost thirty years that experts advocate the need for high-quality studies [11, 51, 59–62], and meta-analyses showed controversial results depending on the molecule investigated [47, 63–65].

Septic Shock

In septic shock, vasoactive medications are generally administered to increase MAP, rather than to improve CO [66]. Indeed, several large RCTs compared different vasoconstrictors in the setting of septic shock, showing no clear superiority of one agent over another [67–72]. Although the classical view of septic cardiovascular dysfunction is that of distributive shock with loss of peripheral vascular resistance and normal or increased CO [73], the role of septic myocardial dysfunction is being increasingly recognized [74, 75]. Several trials comparing vasoactive agents against each other are available [76–78]. We are aware of only one small RCT comparing an inoconstrictor with no vasoactive therapy [79], while only few trials compare inodilators against each other or against placebo [78]. However none of them has been designed to address a difference in survival. Levosimendan is the only inotropic agent that has been investigated a multicenter RCT, with organ function as primary outcome and short-term survival as secondary outcome (details on the Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis [LeoPARDS] trial are provided below) [80, 81]. Nevertheless, mRCTs comparing higher versus lower MAP targets (and hence greater versus lower exposure to exogenous vasopressors) for septic shock patients showed no difference in mortality, although trends towards lower mortality but higher rate of AKI were generally observed in the low-MAP groups [82, 83]. As of today, experts recommend the use of norepinephrine as first line vasopressor in septic shock, while dobutamine or epinephrine are recommended in case of concomitant myocardial dysfunction with low CO or evidence of hypoperfusion despite intravascular volume and MAP optimization, although they acknowledge the low grade of evidence for this recommendation [66].

Acute Heart Failure

Acute heart failure in non-cardiac surgical settings is currently carrying the highest controversies regarding inotropes use. Most of the observational trials which found association between inotropes administration and increased mortality were performed in acute heart failure setting [33–39]. Nevertheless, almost 20% of patients hospitalized for heart

failure still receive treatment with inotropes [84]. Surprisingly, even in this controversial setting, only few, large, multicenter RCTs have been performed. As for cardiac surgery, the largest number of trials investigate levosimendan [85–89], with the notable exception of the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study, which investigate milrinone [90]. Interestingly, none of these studies showed that inotropes use is associated with increased mortality, nor demonstrated a benefit of non-adrenergic agents over dobutamine. Of note, the OPTIME-CHF study, which compared milrinone versus placebo and showed an increase in hypotensive episodes and arrhythmias in the milrinone-treated group, and a non-significant trend towards increased 60-day mortality, enrolled patients judged to not require inotropic treatment. While for mild cases of acute heart failure inotrope use remains controversial, an observational study suggests that, in patients with cardiogenic shock (the most severe form of acute heart failure), adding an inodilator to treatment might actually improve survival [91].

Non-Cardiac Surgery

There are only few studies investigating in isolation the use of inotropes in non-cardiac surgery [47], as a large number of RCTs rather investigated the effect of goal-directed hemodynamic therapy (GDT) [92–94]. GDT consists of a bundle of provisions, including administration of variable combinations of fluids, inotropes/vasopressors and blood products, according to a specific protocol aimed at specific hemodynamic or tissue perfusion indexes targets, performed during the first hours following a surgical procedure. In this context, there is general agreement that GDT may improve survival or at least reduce complications in patients undergoing high-risk surgery [94–98]. Interestingly, GDT seems to reduce also cardiac complications, which, at least in theory, may increase when catecholamines are administered [99]. Importantly, no evidence of harm from treatment with inotropes or vasopressors when used in context of perioperative GDT emerged so far. Nevertheless, the question of whether inotropes in addition to fluids provide increasing benefit remains open according to some authors [100].

Specific Molecules

In this section, we will review the latest evidence on specific inotropes/vasopressors used in clinical practice in intensive care medicine, with focus on most recent or largest RCTs and meta-analyses. A detailed review of pharmacology of inotropes and vasopressors is beyond the scope of this article, and readers are referred to other specific reviews on the topic [7, 8, 12–16]. Readers are referred to other reviews also for vasopressors use during cardiopulmonary resuscitation [101].

Major findings are summarized in Table 2.

Catecholamines

Catecholamines are usually the first-line vasoactive drugs administered to critically ill, hemodynamically unstable patients, as recommended by several professional experts and guidelines for different clinical contexts [51, 66, 102–106]. Among catecholamines, the most commonly used agents are norepinephrine, dopamine, dobutamine and epinephrine [14].

Norepinephrine is the first-line vasopressor recommended by the most important guidelines to restore MAP in all clinical contexts [66, 102, 103]. An interesting observational study performed in United States assessed patients outcome during a period of norepinephrine shortage, and showed that unavailability of norepinephrine was associated with increased mortality despite use of alternative agents [107]. Norepinephrine has been studied in several multicenter RCTs against dopamine, epinephrine, and vasopressin [67–69, 71, 108, 109]. Collectively, these studies showed no differences in survival between norepinephrine and other agents. In the Sepsis Occurrence in Acutely Ill Patients II (SOAP-II) trial, 1679 patients requiring vasopressors were randomized to receive norepinephrine or dopamine [67]. The Authors found no difference in 28-days or 1-year survival in the overall study population. However, norepinephrine use was associated with lower incidence of arrhythmias, and a higher survival rates in the subgroup of patients with cardiogenic shock. Improvement in survival associated with norepinephrine use as compared with dopamine has been confirmed in meta-analyses of RCTs mostly including septic shock trials [110, 111].

Epinephrine is commonly used in critically ill patients as second-line or alternative vasopressor, especially in low-income settings [66]. Traditionally, epinephrine is considered more an inotrope than a vasoconstrictor, while the opposite is true for norepinephrine. Accordingly, epinephrine has been generally considered to be preferrable in the setting of myocardial dysfunction, while norepinephrine is generally considered contraindicated due to concerns of potential decrease in cardiac output due to afterload increase. However, recent evidence from observational studies suggested that epinephrine use may be associated with increased mortality in patients with cardiogenic shock [112, 113]. Nevertheless, a recent meta-analysis of RCTs did not find evidence of increased mortality associated with epinephrine use [114]. The systematic review, however, also underlined the very limited number of RCTs performed in the setting of cardiogenic shock.

Table 2. Summary of current evidence from multicenter randomized controlled trials on the effect of commonly used inotropes/vasopressors on outcomes of critically ill patients.
Modified from Belletti et al.

Drug	Setting	Effect on survival	Additional findings
Norepinephrine	Shock of any etiology	No improvement	Lower incidence of arrhythmias as compared with dopamine. Lower lactate levels as compared with epinephrine.
	Sepsis/vasodilatory shock	No improvement as compared with vasopressin/terlipressin/epinephrine	
	Cardiogenic shock	Possible higher survival as compared with dopamine. No improvement and trend towards increased survival as compared with epinephrine (study not powered to detect mortality difference).	Lower lactate levels as compared with epinephrine. Lower CI (with similar stroke volume but lower heart rate) as compared with epinephrine.
Epinephrine	Shock of any etiology	No improvement	Higher lactate level as compared with norepinephrine (± dobutamine).
	Sepsis	No improvement	Higher lactate level as compared with norepinephrine (± dobutamine).
	Cardiogenic shock	No improvement. Trend towards increased mortality (study not powered to detect mortality difference).	Possible trend towards higher rate of refractory shock. Higher lactate levels as compared with norepinephrine. Higher CI (with similar stroke volume but higher heart rate) as compared with norepinephrine.
Dopamine	Shock of any etiology	No overall improvement. Possible lower survival as compared with norepinephrine in cardiogenic shock.	Higher rate of arrhytmias as compared with norepinephrine.
Vasopressin	Sepsis	No improvement	Possible reduction in need for RRT. Possible reduction in norepinephrine requirements.
Angiotensin II	Vasodilatory shock	No overall improvement (study not powered to detect mortality difference). Possible improvement in survival in patients receiving RRT.	Improvement in MAP. Possible increase in thrombotic adverse events.
Levosimendan	Acutely decompensated heart failure	No improvement	Reduction in BNP and improvement in symptoms.
	Cardiac surgery	No improvement	Reduction in need for catecholamines and incidence of perioperative LCOS. Possible improvement in survival in patients with very low LVEF (⩽25%) undergoing CABG.
	Sepsis	No improvement	Improvement in cardiovascular SOFA score. Increased risk of arrhythmias and hypotension.
Milrinone	Acutely decompensated heart failure	No improvement Possible increase in mortality in patients with ischemic heart failure	Increased risk of arrhythmias and hypotension.
	Cardiac surgery	No improvement (study not powered to detect mortality difference)	Lower CI (with similar stroke volume but lower heart rate), lower PCWP, lower MAP, and lower incidence of AF as compared with dobutamine.
Terlipressin	Sepsis	No improvement	Increase in serious adverse events

Note. AF — atrial fibrillation; BNP — b-type natriuretic pepetide; CABG — coronary artery bypass graft; CI — cardiac index; LCOS — low cardiac output syndrome; LVEF — left ventricular ejection fraction; MAP — mean arterial pressure; PCWP — pulmonary capillary wedge pressure; RRT — renal-replacement therapy; SOFA — sequential organ failure assessment.

In a recent, interesting study by Levy et al., epinephrine was directly compared against norepinephrine in 57 patients with cardiogenic shock due to acute myocardial infarction [109].

The trial was interrupted early due to safety concerns because of a higher incidence of refractory shock and a trend towards increased mortality in the epinephrine group. Furthermore, hemodynamic data collected in the trial showed that while epinephrine actually increases cardiac index more than norepinephrine, this is driven by an increase in heart rate, while measured stroke volume remains similar. This might be relevant in the context of myocardial ischemia, as heart rate is a major determinant of myocardial oxygen consumption. However, it should be noted that very high dose of catecholamines (0.6-0.7 μg/kg/min) were used in this trial. One may argue that with this dose, subtle pharmacological differences between the drugs may become irrelevant. The trial has some limitations, such as including

lactate as a component of a safety outcome of «refractory shock» despite the well-known effect of epinephrine on lactate and higher lactate levels at baseline in the epinephrine group. These results challenge the notion that norepinephrine is detrimental in AMI-related cardiogenic shock, and provide a background for its use in this clinical setting, and for further studies of norepinephrine in patients with myocardial dysfunction [115].

Vasopressin and Terlipressin

Vasopressin is a pure vasoconstrictor that has become increasingly used in recent years as an alternative to norepinephrine.

A first, large RCT comparing vasopressin versus norepinephrine in septic shock was the Vasopressin and Septic Shock Trial (VASST) published in 2008 [68]. In this study, 778 patients with septic shock requiring 5 μg/min of norepinephrine were randomized to vasopressin or norepinephrine on top of open-label vasopressor.

The study showed that vasopressin improve MAP and reduce requirements of concomitant vasopressors, but with no effect on mortality. However, subgroup and post-hoc analyses suggested that vasopressin, especially in combination with steroids, may reduce mortality and acute kidney injury in patients with less severe shock [116, 117]. Accordingly, a 2×2 factorial trial investigating the effect of vasopressin and hydrocortisone in early septic shock (Vasopressin vs Norepinephrine as Initial Therapy in Septic Shock, VANISH) trial was designed [118].

This subsequent RCT enrolling 409 patients with early septic shock [71] showed no difference in mortality, a lower rate of need for renal-replacement therapy (RRT) in the vasopressin group (but driven by reduction in RRT only in non-survivors), and a higher rate of digital and myocardial ischemia in the vasopressin group. Taken together, these data suggest that vasopressin does effectively increase blood pressure and reduce norepinephrine requirements, but with no significant effects on major outcomes and with the potential to increase adverse events. The only potential benefit may be on renal function, as also suggested by a recent single-center RCT performed in the setting of post-cardiotomy vasoplegic shock [119].

Similarly, terlipressin (a long-acting analogue of vasopressin), despite some promising early results [120–123], failed to show improvement in outcomes in a recent mRCT of 617 patients [70]. On the contrary, terlipressin use increased rate of adverse events.

Phosphodiesterase 3-inhibitors

Phosphodiesterase-3 inhibitors are inodilators frequently used as inotropic agents in patients with LCOS, especially in patients receiving chronic beta-blocker therapy [103, 124–127]. They are generally considered as an alternative to catecholamines, or as agents with synergistic action in patients requiring high-dose inotropic support.

In the previously mentioned OPTIME-CHF study, patients with acutely decompensated heart failure but without shock were randomized to receive milrinone or placebo [90, 128]. Patients in the milrinone group had a higher rate of hypotension and arrhythmias, without differences in major outcomes. An interesting post-hoc analysis suggested that milrinone may worsen outcome in patients with ischemic heart failure, while it may be beneficial in patients with other causes of heart failure [28].

Another multicenter RCT performed in the setting of cardiac surgery compared milrinone versus dobutamine in patients with LCOS after cardiac surgery [129]. The study focused on hemodynamic rather than clinical endpoints, and showed that dobutamine was associated with higher cardiac index (driven by a greater increase in heart rate), higher MAP, and higher incidence of atrial fibrillation, while milrinone was associated with greater decrease in pulmonary capillary wedge pressure.

More recently, a single-center study randomized 192 patients with cardiogenic shock (Society of Cardiovascular Angiography and Interventions [SCAI]-stage B or higher [130]) to receive milrinone or dobutamine as primary inotropic agent (Dobutamine Compared to Milrinone [DOREMI] study) [131]. The Authors found no difference in terms of mortality, adverse events, hemodynamic parameters or need for vasopressors. Collectively, these studies confirm the hemodynamic efficacy of milrinone, but demonstrate neutral effects on clinical outcomes, as compared with catecholamines.

Interestingly, a recent experimental, physiologic study showed that milrinone has no direct inotropic effect when tested in conditions independent from pre- and afterload. Accordingly, the authors hypothesized that the increase in cardiac output observed with PDE-3 inhibitors may be related to their pre- and afterload modulation properties, rather than a direct inotropic effect [132]. This might also explain the greater effect on PCWP observed as compared with dobutamine.

Levosimendan

Levosimendan is a calcium-sensitizer and PDE-3 inhibitor that has been extensively investigated as inotropic agent in recent years. Indeed, it is the most investigated inotrope of the last 30 years, with more than 100 RCTs including almost 10000 patients [47].

Several RCTs and meta-analyses suggested a mortality benefit with levosimendan administration in a wide variety of clinical settings [133].

In the past years, several mRCTs has been conducted in the settings of acute heart failure, cardiac

surgery and sepsis [56-58, 80, 81, 87, 88, 134–136]. Collectively, all of these studies failed to show a beneficial effect of levosimendan on mortality or other major clinical outcomes. These studies showed that levosimendan administration is associated with a reduction in need for other concomitant inotropes and higher rate of hypotension (results that are consistent with its inodilator effect) and arrhythmias. The only potential beneficial effect has been suggested for the limited group of patients with very low left ventricular ejection fraction undergoing CABG, when administered prophylactically [137], and for patients on chronic beta-blocker therapy [138].

Interestingly, while traditionally considered a calcium-sensitizer, some experimental studies challenged this view and suggested that the inotropic effects of levosimendan are almost exclusively related to its PDE-3 inhibitor effect [139], and potentially to its effect on vascular K^+-ATP channels [16].

Angiotensin II

Angiotensin II is a potent pure vasoconstrictor that has been increasingly studied in recent years and suggested as a potential catecholamine-sparing agent for patients with vasodilatory shock.

In the largest and most recent mRCT performed, 344 patients with vasodilatory shock requiring high-dose norepinephrine and with normal cardiac index were randomized to receive angiotensin II or placebo on top of open-label norepinephrine [140]. The study showed that angiotensin II effectively increases MAP and reduces norepinephrine requirements. Although the study was underpowered to detect outcome differences, no hints for benefit or harms were reported. A subgroup analysis focusing on patients with need for RRT suggested that angiotensin II may be particularly beneficial in this subgroup of patients in terms of mortality and renal recovery [141]. However, these findings require further investigations. Of note, a potential increase in adverse events such as decreased cardiac output, thrombotic events, delirium and fungal infections has been associated with angiotensin II use [9, 10, 142].

Discussion

Despite concerns raised regarding their safety, inotropes are still widely used in critically ill patients. There are currently controversies in evidences since the increase in mortality associated with inotropes use reported in observational trials have not yet found confirm in RCTs. This attitude of physician may derive from the fact that, despite evidences from observational studied, RCTs have not yet shown an increase in mortality associated with inotropes use. Limits of observational trials are well known. Even with the best statistical methods, unreported clinical data may render correct matching of cases and controls impossible also when baseline characteristics are apparently similar. For example, several recently published meta-analyses showed that the association between a liberal transfusion strategy and mortality in cardiac surgery suggested by a large number of observational trials was not find confirm in RCTs [143, 144]. Patients requiring inotropic support are usually the most severely ill, with increasing doses of inotropes usually indicating increase disease severity [145]. In such a context, it may be very easy to find an association between inotropes use and increased mortality, yet determining the exact cause-effect relationship might be very difficult. Multicenter RCTs and meta-analyses of RCTs are currently considered by clinical scientists to provide the highest level of evidence regarding the effectiveness of a given treatment [146, 147]. Unfortunately, mRCT in critical care setting often provide neutral or contradicting results, with only few trials associated with a clear indication towards benefit or harm of a specific intervention [148–153]. These discouraging results may derive from true lack of effect, but also from organizational problems, patients heterogeneity, limited statistical power, or by difficulties in applying standardized protocols in the highly dynamic and variable setting of intensive care medicine [152, 154].

An important limitations of trials on inotropes use is that, unless they directly compare an inotrope against another, they generally exclude the most severely ill patients. This is because, in the history of critical illness, there is often a «turning point» at which the feeling of clinicians that treatment with inotropes is keeping the patients alive becomes so strong, that withholding such treatment would be unethical. In such a context, designing and conducting a trial comparing an intervention with no intervention would be really challenging from an ethical point of view [155]. Indeed, despite all concerns raised regarding safety of inotropes treatment, there is no trial randomizing patients judged to require treatment with inotropes to inotropes administration or no inotropes at all [47]. Indirect evidence may derive from studies investigating «liberal» (or higher) versus «restrictive» (or lower) hemodynamic targets (e. g. high vs low MAP, high vs low CO). Collectively, these studies suggested that higher targets (and hence greater use of interventions including fluids, vasopressors, and inotropes) are generally not necessary and sometimes may be harmful [82, 83, 156–158]. Indeed, future studies should probably focus on defining optimal hemodynamic targets, rather than comparing one molecule against another.

In the future, increasing clinical experience and technological advances in mechanical circulatory support (MCS) devices might change this situation and allow comparison between a pharmacological and a mechanical treatment; however it doesn't seem that this will happen in the short period, as use of

MCS still require a huge amount of expertise and resources, and MCS devices are still associated with several complications that requires careful weighting of benefit and risks in each single case [159–161]. Nevertheless, some pilot studies are now being performed and showed promising results in favor of MCS [162]. In addition, the recently developed concept of «mechanical unloading» as a new paradigm to improve outcome in heart failure and cardiogenic shock is gaining increasing popularity [163–165]. In general, mechanical circulatory support should be considered early in case of dependency on high-dose inotropes/vasopressor (especially with vasoactive-inotropic score [VIS] [145] >20).

Notably, even in patients with chronic heart failure, when disease reach an advanced phase available studies did not show a clear increase in mortality associated with inotropes use [166]. On the contrary, the definition of «inotrope-dependent» heart failure is widely used, particularly for patients waiting for therapy with either long-term ventricular assist devices (VAD) or heart transplantation [167, 168]. As correctly underlined by Guglin and Kaufman, if a patient cannot be weaned off inotropes because of inacceptable worsening organ function than we have to accept that inotropes prolong life [166]. In cardiac surgery, patients will often experience a potential life-threatening post-operative depression of cardiac function which is however likely to improve in few hours [169]. However, the LCOS associated with post-operative myocardial stunning or afterload mismatch might lead to multiorgan failure and death before spontaneous recovery occur, and temporary support with inotropes could allow patients to survive this critical phase [170, 171].

Therefore, according to current evidence, it seems that the question should not be whether inotropes increase mortality or not; we should instead focus our research in determining which patients and at which disease time-point will benefit from treatment with inotropes, and when, on the contrary, our treatment is harmful or futile [172, 173]. For example, Kastrup and colleagues observed that, while prolonged treatment with epinephrine and norepinephrine above a certain threshold is associated with poor survival rates, short-term use of high doses of these drugs was not linked to increased mortality [174]. In another interesting study, Prys-Pricard et al found that only 9% of critically ill patients receiving three or more vasoactive drugs survived to hospital discharge [175]. All of these surviving patients have received inotropic therapy, but, above all, all of these received an intervention aimed at correcting the underlying cause of cardiovascular dysfunction (e.g. surgery for control of infection source, myocardial revascularization, or heart transplantation). Early myocardial revascularization is, indeed, one of the very few treatment demonstrated in a RCT to improve survival in patients with cardiogenic shock following acute myocardial infarction [176–178]. All these studies suggest us that, regardless of the intensity of pharmacological inotropic support, unless the primary cause of hemodynamic instability could be treated, outcome will be poor. Patients whose ultimate cause for hemodynamic compromise can not be treated, will likely require prolonged treatment with increasing-dose of vasoactive drugs, thereby influencing results of observational trials on inotropes use.

To add further complexity, hemodynamic management of critically ill patients is not as easy as a simple decision to use or not inotropes. There is a complex interaction between fluids requirement and administration, pre-existing and new-onset cardiovascular and renal disease, and treatment with vasoactive drugs which often need to be carefully evaluated for each single patient, and continuously reviewed as treatment progresses [179–181]. After all, the strongest evidences in favor of inotropes use are in the setting of perioperative goal-directed hemodynamic optimization, which requires a combination of fluids, inotropes and appropriate hemodynamic monitoring aimed at reaching specific target parameters while avoiding unnecessary, excessive drug administration. Cardiopulmonary interaction and hemodynamic effects of mechanical ventilation should also be considered, especially in patients with both cardiovascular and respiratory failure [182, 184].

A greater attention has been given in recent years towards so-called metabolic resuscitation for patients with cardiovascular failure. Metabolic resuscitation includes a combination of steroids and vitamins (Vitamin C and vitamin B1) and a large number of RCTs has been performed to test these agents or combination of agents [185, 186]. Collectively, current evidence suggest that metabolic resuscitation does not provide survival benefit, with the potential exception of high-dose vitamin C [186]. Nevertheless, steroids administration in patients with septic shock reduces duration of vasopressor therapy and length of stay in ICU without increasing adverse events [186]. Additional areas of investigation include various alternative «metabolic» strategies of myocardial protection including amino acids and insulin-potassium-glucose [187–190], which are currently under investigation.

While hemodynamic management traditionally focused on macrocirculation and gross hemodynamic parameters (such as MAP), the role of microcirculatory dysfunction during critical illness is being increasingly recognized as a determinant of outcome [191]. As a result, the effect of the different agents is being investigated, and there are some evidences that inodilators may improve microcirculatory function and ultimately effective tissue perfusion, as compared

Table 3. Summary of current major evidence and concepts on inotropes/vasopressor use in critically ill patients.

Catecholamines (norepinephrine) remain first-line agents in almost every setting
Achievement of adequate hemodynamic goals is probably more important than molecules
Supraphysiological hemodynamic targets are harmful, restrictive targets (e.g. permissive hypotension) may be acceptable in several cases
Norepinephrine shortage is detrimental
Dopamine (high-dose) is detrimental
Vasopressin and angiotensin II reduce norepinephrine requirements, increase MAP but do not improve outcomes
PDE-3 inhibitors and levosimendan are not superior to catecholamines
Steroids reduce vasopressor requirements in septic shock and may improve survival
Interaction with preload/afterload/fluids/mechanical ventilation is important and under-investigated
Chose a simple inotropic-vasoconstrictor combination for your department and be ready to change it quickly if the patient is a non-responder or develops side effects
Consider early mechanical circulatory support (especially with VIS>20)

Note. MAP — mean arterial pressure; PDE-3 — phosphodiesterase-3; VIS — vasoactive-inotropic score.

with vasoconstrictors or inoconstrictors [78, 91, 192–194]. Future research should focus on the different effect of vasoactive medications on microcirculation and tissue perfusion independently of traditional hemodynamic parameters.

Finally, a new concept of «broad-spectrum vasopressors» has been recently described [195]. As for broad-spectrum antibiotic therapy, some experts suggest combination use of different vasopressors with different mechanism of action (e. g. norepinephrine, vasopressin and angiotensin II) to reduce the dose of each drug and limit side effects. Whether this concept translated into greater clinical benefit remains to be determined. Table 3 provides a final take-home message on inotropes and vasopressors use in critical care.

Conclusions

Inotropes are powerful drugs with relevant side effects that need to be known and acknowledged, and incorrect prescription of inotropes administration can increase morbidity and mortality Determination of when, to whom and how administer inotropes is of utmost importance to correctly manage critically ill patients.

The choice of molecule or combination of molecules does not seem to influence outcome as long as comparable hemodynamic parameters are obtained. Clinicians should chose the drug or combination of drugs they are most familiar with.

Future studies should focus on interaction with vasoactive drugs, fluids, pre-load and afterload, optimal timing of vasoactive initiations, and the role of MCS.

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