Inodilators in septic shock: should these be used?

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Abstract: Septic shock involves a complex interaction between abnormal vasodilation, relative and/or absolute hypovolemia, myocardial dysfunction, and altered blood flow distribution to the tissues. Fluid administration, vasopressor support and inotropes, represent fundamental pieces of quantitative resuscitation protocols directed to assist the restoration of impaired tissue perfusion during septic shock. Indeed, current recommendations on sepsis management include the use of inotropes in the case of myocardial dysfunction, as suggested by a low cardiac output, increased filling pressures, or persisting signals of tissue hypoperfusion despite an adequate correction of intravascular volume and mean arterial pressure by fluid administration and vasopressor support. Evidence supporting the use of inotropes in sepsis and septic shock is mainly based on physiological studies. Most of them suggest a beneficial effect of inotropes on macro hemodynamics especially when sepsis coexists with myocardial dysfunction; others, however, have demonstrated variable results on regional splanchnic circulation, while others suggest favorable effects on microvascular distribution independently of its impact on cardiac output. Conversely, impact of inodilators on clinical outcomes in this context has been more controversial. Use of dobutamine has not been consistently related with more favorable clinical results, while systematic administration of levosimendan in sepsis do not prevent the development of multiorgan dysfunction, even in patients with evidence of myocardial dysfunction. Nevertheless, a recent metanalysis of clinical studies suggests that cardiovascular support regimens based on inodilators in sepsis and septic shock could provide some beneficial effect on mortality, while other one corroborated such effect on mortality specially in patients with proved lower cardiac output. Thus, using or not inotropes during sepsis and septic shock remains as controversy matter that deserves more research efforts.

Keywords: Sepsis; septic shock; inotropes; inodilators; dobutamine; levosimendan; phosphodiesterase inhibitors; microcirculation; clinical outcomes

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Introduction

Early recognition and prompt reversal of sepsis-induced tissue hypoperfusion are key elements in the management of septic shock (1,2). In this regard, quantitative resuscitation protocols based on fluid administration, vasopressor support and inotropes, represent the core of therapy directed to restore macro and microcirculatory derangements occurred during shock (2). Current guidelines on sepsis management recommend the use of dobutamine up to 20 μg/kg·min^{-1} in cases of septic shock and myocardial dysfunction or when signs of hypoperfusion persist despite of an adequate intravascular volume and mean arterial pressure (1). Nevertheless, evidence supporting the use of dobutamine

and other inodilators in sepsis and septic shock is preferably physiologic with most data suggesting beneficial effects on macro hemodynamics and indices of tissue perfusion. Conversely, impact of inodilators on clinical outcomes in this context has been more controversial. However, recent metanalyses suggest that cardiovascular support regimens based on inodilators in sepsis and septic shock could provide some beneficial effect on mortality (3), especially in patients with a lower cardiac output (4). In this review, we will discuss about the physiological and clinical data supporting or not the use of inodilators in septic shock.

Basic pharmacology and mechanisms of action

Dobutamine

Dobutamine used in clinical practice is a racemic mixture of (+) and (–) enantiomers (5). The (–)-enantiomer exerts a potent pressor activity mediated by alpha-1 stimulation and also produces marked increases in cardiac output, stroke volume, total peripheral resistance and mean arterial pressure, but does not induce significant increases in heart rate (6). Conversely, the (+)-enantiomer is a potent alpha-1 antagonist able to counteract the effects of the (–)-enantiomer on these receptors. Moreover, the (+)-enantiomer posses a predominant beta-1 and beta-2 agonist activity which leads to increase cardiac output and to reduce total peripheral vascular resistance and mean arterial pressure (7). Nevertheless, as racemic mixture, pharmacological activity of the (+/–)-dobutamine will result from the composite effects of the individual stereoisomers (6).

Compared to norepinephrine, the (+/–)-dobutamine exerts more prominent inotropic than chronotropic effects on the heart, with minimal changes in peripheral vascular resistance maybe because the counterbalancing of alpha-1 receptor-mediated vasoconstriction and beta-2 receptor-mediated vasodilation (6). In healthy volunteers, an infusion dose of 2.5 μgr/kg·min^{-1} increased cardiac output due to augmentation in stroke volume by improvement of left ventricular contractility (8). However, at higher plasmatic concentrations (infusion doses ≥5 μgr/kg·min^{-1}), the linear increase of cardiac output relied entirely on increased heart rate since stroke volume did not change or even decreased (8). On the other hand, in critically ill patients, dobutamine might exert a potent dose-dependent vasodilatory effect when administered at doses >10 μgr/kg·min^{-1}. Thus, in a randomized controlled trial targeting supranormal oxygen delivery and oxygen consumption values, patients receiving higher doses of dobutamine also required higher doses of norepinephrine to sustain arterial pressure (9). Nevertheless, in other randomized controlled trial including 330 patients with septic shock, this vasodilatory effect of dobutamine at doses <10 μgr/kg.min^{-1} was not clinically relevant since the dose of vasopressors to sustain arterial pressure was identical in both norepinephrine + dobutamine *vs.* epinephrine groups (10).

Milrinone and other phosphodiesterase 3 (PDE-3) inhibitors

PDE-3 inhibitors such as milrinone or enoximone impede cAMP degradation, thus increasing intracellular cAMP levels and activating the cAMP-PKA pathway. This phenomenon ultimately results in higher peak Ca^{++} concentrations during systole and thereby, myocardial peak force (11). All PDE-3 inhibitors hasten myocardial contraction (positive clinotropic effect) and relaxation (positive lusitropic effect), which allow sufficient perfusion time during diastole, even under catecholamine stimulation and concomitant tachycardia (12). PDE-3 inhibitors also have important vasoactive effects in the peripheral circulation through cAMP-mediated effects on intracellular calcium handling in vascular smooth muscle, resulting in decreased arterial and venous tone. The combination of positive inotropy and mixed arterial and venous dilation effects, led to the designation as "inodilators" (11). This is how despite its inotropic properties, concurrent use of vasopressors is frequently necessary during administration of PDE-3 inhibitors.

Levosimendan and other Ca^{++} sensitizers

Calcium (Ca^{++}) sensitizers augment myocardial contractility by inducing conformational changes in TnC, thus enhancing the sensitivity of troponin-C (TnC) to Ca^{++} (13,14). This potentiating effect increases the extent of actin–myosin interactions at any given concentration of intracellular Ca^{++}, without a substantial increase in myocardial oxygen consumption (15,16). Increased myofilament Ca^{++} sensitivity also causes reduced dissociation of Ca^{++} from the myofilaments in diastole and prolongation of relaxation ("negative lusitropic effect"), which could potentially aggravate the diastolic function in some patients with heart failure. Nevertheless, Ca^{++} sensitizers as levosimendan have additional selective and potent inhibitory effects on PDE-3, whose positive lusitropic consequence appears to antagonize the negative lusitropic effect of Ca^{++} sensitization (17,18).

Meanwhile, in the peripheral circulation, levosimendan activates ATP-sensitive K^+ channels, leading to systemic vasodilation (19,20).

Cardiac myocyte Ca^{++} homeostasis is commonly altered during sepsis and lipopolysaccharide exposure, with serious alterations in cardiac muscle contractility. Nevertheless, it is not clear whether this phenomenon is product of abnormal rapid calcium cycling (which increases myocardial oxygen demand) (21) and decreased myofilament sensitivity to calcium (with subsequent worsening of the myofilament force–calcium relationship) (22) or, simply, sluggish intracellular calcium cycling. In any of these cases, Ca^{++}-sensitizing agents could have theoretical advantages over other inotropes by improving Ca^{++} handling.

Theoretical rationale for using inotropes in patients with septic shock

Pathogenesis of septic shock involves a complex interaction between abnormal vasodilation, relative and/or absolute hypovolemia, myocardial dysfunction, and altered blood flow distribution to the tissues caused by the inflammatory response to infection. Vasopressors and inotropes are used as therapeutic interventions to assist the restoration of impaired tissue perfusion during shock. In this sense, dobutamine and other inotropes have typically been used to increase cardiac output and oxygen transport, aiming to restore cell respiration and aerobic metabolism. According to current recommendations in sepsis management, inotropes should be considered in the case of myocardial dysfunction, as suggested by a low cardiac output, increased filling pressures, or persisting signals of tissue hypoperfusion despite an adequate correction of intravascular volume and targeting mean arterial pressure by fluid administration and vasopressor support (1). Theoretically, inotrope therapy should increase myocardial contractility and then stroke volume, while counterbalancing increases in myocardial oxygen consumption (23) and maintaining the lower filling pressures to ensure adequate downstream pressures to the systemic circulation.

Although cardiac output is usually normal or even high after initial fluid resuscitation, myocardial contractility may be impaired in an important proportion of septic patients (24,25). Such myocardial dysfunction in sepsis is a multifactorial phenomenon that includes the mediation of some pro inflammatory cytokines (26-28), increased nitric oxide synthase expression (29,30), down-regulation of the beta-adrenergic response to catecholamines, but with a preserved myocardial blood flow, net myocardial lactate extraction and diminished coronary artery-to-coronary sinus oxygen difference (31). Whatever the mechanism, myocardial dysfunction has represented the main reason to administering inotropes during septic shock.

An early study using radionuclide scans reported a decreased left ventricular ejection fraction, left ventricle dilation, and preserved stroke volume (32). Interestingly, reversion of such alterations was observed in patients that finally survived (25,32). Other observations suggested abnormal ventricular responses to fluid loading, with lower increases in left ventricular stroke work index than in non-septic controls (33). Subsequent studies using echocardiography found similar decreased ejection fractions, but described less prominent ventricular dilation and low stroke volumes in those patients that finally died (24,25).

An interesting feature of sepsis-induced myocardial dysfunction is that survivors exhibited lower left ventricular ejection fractions and higher end-diastolic volumes, suggesting that ventricular dilatation may confer a "protective" effect during myocardial depression (32). Usually, decreased systolic contractility restricts the ability of the ventricle to eject up to low end-systolic volumes, so stroke volume decreases (31). Nevertheless, falls in stroke volume may be compensated by increasing end-diastolic volume through an adequate fluid resuscitation and by the decreased afterload due to arterial vasodilation. Such compensatory mechanisms can generate a high stroke volume hyperdynamic shock, even systolic contractility is decreased and ejection fraction remains low. Conversely, in the most severe cases, left ventricular afterload is more severely decreased, which provocates low stroke volumes and the contraintuitive phenomennon of preserved ejection fraction in non-survivors.

To add more complexity, diastolic dysfunction can also happen during sepsis and septic shock, thus impairing the ventricular filling (34). Thus, the combination of impaired ability to fill and impaired ejection capacity leads to low stroke volume, hypodynamic and fatal septic shock. Inotropes as dobutamine can potentially increase contractility if systolic dysfunction is present. However, patients with systolic dysfunction are more likely to survive even without dobutamine treatment. Meanwhile, patients with a decreased diastolic compliance are unlikely to benefit from dobutamine, and they are more likely to die and therefore, more prone "to require" therapeutic interventions. Alternatively, levosimendan has been proposed as a treatment for septic myocardial dysfunction

because its ability to increase ventricular contractility without impairing diastolic relaxation. Nevertheless, current clinical evidence does not support its routinely use in septic shock (35).

Cardiovascular failure due to sepsis also involves peripheral vascular dysfunction, which includes arterial and venous vasodilation, impaired regulation of the distribution of arteriolar blood flow, heterogeneity of capillary microcirculatory flow, inflammation involving the endothelium and microcirculation, and increased permeability of vessels with capillary leakage leading to tissue edema and intravascular hypovolemia. In this sense, myocardial dysfunction becomes critical because peripheral vascular dysfunction places much greater demand on the heart. Important misdistribution of flow to the tissues may persist even after optimizing cardiac output because abnormalities in microcirculatory blood flow distribution induced by the inflammatory response. In this regard, low doses of dobutamine have been advocated to improve microcirculatory blood flow even independently of variations in cardiac output (36,37).

Use of specific inotropes in septic shock

Dobutamine

Even though dobutamine is currently recommended in septic shock to improve cardiac output and to correct hypoperfusion, its real clinical benefit has been widely debated. Early studies demonstrated beneficial effects of dobutamine on macro hemodynamics (38-41), hepatic microcirculation (42), splanchnic perfusion and tissue oxygenation (43-47). Nevertheless, effects on macrovascular splanchnic blood flow (48-55), total intestinal microvascular blood flow (43,56), and sublingual microcirculation (36,57,58) have sometimes been conflicting. Conversely, information about the effect of dobutamine on microcirculatory blood flow distribution at intestinal villi during sepsis or endotoxemia has been limited but favorable (37,59). Measurements of total microvascular blood flow and its distribution (i.e., estimation of blood flow heterogeneity) could be more relevant than total mesenteric arterial blood flow measurements (60,61). Interestingly, the favorable effects of low doses of dobutamine on microcirculatory blood flow seems to be dissociated from macro hemodynamics (36,37). Indeed, this apparent "dissociation" between macro and micro hemodynamics during human and experimental septic shock is a phenomenon commonly described in clinical observational studies (36,62-64) and highlighted in expert opinion manuscripts (61,65). Microcirculatory blood flow distribution should be ultimately the determinant of tissue perfusion beyond normalization of macro hemodynamic parameters (61,62,66). In this sense, dobutamine could exert a favorable effect on microvascular blood flow distribution, and this in turn, on the cellular oxygen consumption capabilities at intestinal mucosa (37).

No randomized controlled trials have compared the effects of dobutamine versus placebo on clinical outcomes. Nevertheless, dobutamine has been incorporated in a number of quantitative resuscitation protocols as fundamental piece of the resuscitation strategy. Use of dobutamine was included in the original protocol of early goal-directed therapy (EGDT) in patients with sepsis and septic shock (67). In this study, 15.54% of patients assigned to the EGDT group received dobutamine within the first 72 hours. Although EGDT group was related with a significant decrease of in-hospital, 28 and 60-day mortality, the direct impact of dobutamine on final results is not possible to discern (67). Nevertheless, no significant increases of adverse effects linked to dobutamine were there reported (67). Subsequent randomized controlled trials on EGDT in septic shock, failed to demonstrate a clinical benefit with such strategy (68-70). In these trials, use of dobutamine was significantly higher in EGDT than in standard care groups (ProCESS trial 8.0 *vs.* 1.1%, respectively; P<0.001; ProMISe trial 8.0 *vs.* 1.1%, respectively; P<0.001; and ARISE trial 15.4 *vs.* 2.6%, respectively; P<0.0001). Again, no significant adverse events could be attributed to the use of dobutamine (68-70). Other multicenter, randomized controlled trial compared the combination of dobutamine plus norepinephrine *vs.* epinephrine in 330 patients with septic shock (10). There were no significant differences in all-cause mortality rate at day-28 and no significant differences in vasopressor requirements or adverse effects were observed between study groups. Nevertheless, the group assigned to dobutamine plus norepinephrine evolved with lower lactate and glucose levels during the experimental period (10).

Finally, a recent metanalysis demonstrated that combination of norepinephrine and dobutamine is associated with a reduction in mortality at day-28 in patients with septic shock and low cardiac output (4), while other one suggested that regimens based on inodilators in septic shock have the highest possibility to improve survival (3). Thus, after years of fruitless attempts to prove the clinical benefit of dobutamine, the results of these metanalyses

apparently support the use of dobutamine in patients with septic shock. Nevertheless, results of such metanalyses should be considered carefully since heterogeneity of the studies included remains substantially high.

Levosimendan

Use of levosimendan has been related with beneficial effects in acute and chronic cardiac failure and in cardiac perioperative patients (71,72). However, despite the potential advantages based on its mechanism of action, its value in septic shock remains highly debatable. In an experimental model of sepsis, levosimendan was superior to dobutamine and milrinone in restoring cardiac function (73). Other experimental data suggest that levosimendan could modulate inflammatory response by downregulating nuclear factor kappa-beta (NF-κβ)-dependent transcription (74), inhibiting inducible nitric oxide synthase promoter activity and reducing NO expression (75). An experimental model of sepsis suggested that levosimendan and norepinephrine had comparable effects in restoring cardiac output but without significant influence on microcirculatory blood flow (76). Nevertheless, levosimendan was related with better oxygen partial pressure (pO_2) at tissue level (76). Both human and experimental studies revealed a beneficial effect of levosimendan on hepatic flow, sublingual microcirculation and intestinal intramucosal acidosis (77-79).

An early prospective randomized controlled trial studied the systemic and regional hemodynamics in 28 patients with septic shock and depressed left ventricular ejection fraction (LVEF <45%) after 48 hours of conventional treatment. Levosimendan increased LVEF, decreased left ventricular end-diastolic volume, increased gastric mucosal flow and creatinine clearance while induced a faster lactate normalization (80). Nevertheless, in the levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis (LeoPARDS) trial (81), which studied the effects of this drug in 515 patients with septic shock, the addition of levosimendan to standard management did not result in less severe organ dysfunction or mortality (81). This trial recruited a wide range of patients with septic shock, so the lack of benefit of levosimendan was attributed to the fact that not all patients had cardiac dysfunction (82). However, a subsequent subanalysis of the data from the LeoPARDS study confirmed the lack of benefit of levosimendan in patients with biochemical evidence of cardiac dysfunction evidenced by high N-terminal prohormone of brain natriuretic peptide (NT-proBNP), troponin I (cTnI) and other five inflammatory mediators (83). Other study evaluating the effects of levosimendan on organ dysfunction in a population of elderly patients with sepsis also revealed no benefit of levosimendan on the development of organ failure (84).

Metanalyses on the effects of levosimendan in patients with sepsis and septic shock have yielded contradictory results. A metanalysis depicted favorable results of levosimendan in septic shock in comparison with standard inotropic therapy (85). Nevertheless, a recent metanalysis including 10 studies and 1,036 patients with sepsis and septic shock demonstrated a lack of benefit of levosimendan on mortality (OR 0.89, 95% CI, 0.69 to 1.16, P=0.39), although levosimendan was related with a more effective reduction in lactate levels and improvement of cardiac function (35). No significant benefit on mortality was observed when the use of levosimendan was compared with dobutamine in patients with demonstrated cardiac dysfunction (35). Similarly, other recent metanalysis suggested that there is no evidence of superiority of levosimendan over dobutamine in patients with sepsis and septic shock (86). Nevertheless, these authors found a significant amount of heterogeneity in mortality data, which hinder the interpretation of the data.

PDE-3 inhibitors

Most of the information of the use of milrinone in sepsis and septic shock come from pediatric populations. Early studies demonstrated that milrinone (87) and amrinone (88) might improve cardiovascular function in pediatric patients with septic shock. Milrinone also exhibited beneficial effects in patients with meningococcal sepsis and purpura with severe peripheral vasoconstriction (89). In experimental sepsis, milrinone improved central venous saturation and lactate levels when compared with placebo (90). In the same line, milrinone demonstrated to attenuate arteriolar vasoconstriction and to improve functional capillary density in an experimental endotoxemic model (91). An *in vitro* study in cardiomyocyte cultures treated with lipopolysaccharide or tumor necrosis factor-alpha, alone or in presence of amrinone or milrinone, demonstrated a significant reduction of nuclear factor kappa-beta (NF-κβ) and pro-inflammatory cytokines (92).

All PDE-3 inhibitors have vasodilatory effects that might exacerbate hypotension in sepsis, whereby their use in this condition might theoretically cause harm. There is no metanalysis evaluating the effects of milrinone on clinical outcomes in patients with sepsis or septic shock.

Conclusions

Inotropes should be considered in cases of sepsis and septic shock with evidence of myocardial dysfunction or persisting signals of tissue hypoperfusion despite an adequate correction of intravascular volume and targeting mean arterial pressure by fluid administration and vasopressor support. Use of inotropes is mostly based on physiological data. Nevertheless, recent metanalyses suggest that regimens using inotropes could provide some benefit on mortality, especially in patients with cardiac dysfunction.

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