
Inotropic Support in the Treatment of Septic Myocardial Dysfunction: Pathophysiological Implications Supporting the Use of Levosimendan

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Introduction

Myocardial dysfunction is a frequent organ manifestation during septic shock and the subsequent impairment in cardiac output may result in organ hypoperfusion, requiring prompt and adequate treatment to restore cardiovascular function and reverse shock [1]. Current sepsis guidelines recommend resuscitation with intravascular fluid administration in association with inotropes and vasopressors to maintain organ perfusion [2]. Dobutamine is recommended as first-line inotropic agent and should be administered when low cardiac output or signs of hypoperfusion persist after adequate fluid resuscitation and perfusion pressure have been achieved [2]. However, the efficacy of dobutamine in patients with heart failure has not been fully demonstrated and concerns on its use are still present [3]. Although dobutamine improves perfusion and increases oxygen delivery (DO_2), its impact on survival in septic shock patients is limited, with guideline recommendations based mainly on the landmark study by Rivers et al. [4]. Recently, Wilkman et al. [5] reported that the use of inotropes, particularly dobutamine, in septic shock was associated with increased 90-day mortality. In explaining the lack of outcome benefit [3, 5], several aspects need to be taken into account. First, the need of inotropic support may simply represent an expression of disease severity rather than the cause of a poor outcome. Second, whereas the treatment of impaired cardiac output should be tailored based on the etiological mechanism of the cardiovascular dysfunction, the current guidelines recommend the use of inotropes without differentiating the un-

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Fig. 1 Left ventricular outflow tract. **a** normal; **b** significant left ventricular outflow tract obstruction due to systolic anterior motion of the mitral apparatus. In presence of this alteration, the administration of inotropes may worsen systemic hemodynamics

derlying causes of impaired left ventricular (LV) stroke volume [2, 6]. In addition, the majority of cardiovascular monitoring instruments provide data almost exclusively on cardiac output and pressures. This approach may potentially increase the number of patients who may be harmed by inotrope administration (Fig. 1). Finally, the beneficial short-term effect of enhanced contractility by cAMP-increasing drugs (e. g., dobutamine, milrinone) is, at least partly, abolished by the increased energy consumption, the worsening of ventricular relaxation and the direct cardiomyocyte toxicity [1, 7–10].

On this basis, a wider use of echocardiography to better define septic myocardial dysfunction and an alternative to catecholaminergic inotropes with less harmful effects may contribute to improving septic myocardial dysfunction. Promising new inotropes that have been developed for patients with heart failure are of potential interest for patients with sepsis-related myocardial dysfunction, although future studies are needed before these drugs can be considered for clinical use (Table 1). In recent years, much attention has been paid to the use of the calcium sensitizer, levosimendan, in the treatment of septic myocardial dysfunction [11–16]. The aim of this chapter is, therefore, to provide an overview on the pathophysiology of sepsis-induced cardiac dysfunction and how it may support the use of levosimendan in the clinical management of affected patients.

Table 1 Inotropes currently used in clinical practice and new drugs under investigation

Inotropic mechanism	Drugs
Sodium-potassium-ATPase inhibition	Digoxin
β -adrenoceptor stimulation	Dobutamine, dopamine, epinephrine
Phosphodiesterase inhibition	Enoximone, milrinone
Calcium sensitization	Levosimendan
Sodium-potassium-ATPase inhibition plus SERCA activation	Istaroxime
Acto-myosin cross-bridge activation	Omecamtiv mecarbil
SERCA activation	Gene transfer
SERCA activation plus vasodilation	Nitroxyl donor; CXL-1020
Ryanodine receptor stabilization	Ryanodine receptor stabilizer; S44121
Energetic modulation	Etomoxir, pyruvate

SERCA: sarcoendoplasmic reticulum calcium ATPase

Mechanisms of Action and Clinical Implications

Inotropism

The underlying mechanisms of sepsis-induced cardiac dysfunction and the pharmacological features of levosimendan [1, 16] both suggest that this alternative inodilator might be a useful drug in the presence of depressed contractility, with potential advantages compared with conventional catecholamines. One of the key feature of the early phase of septic shock is massive sympathetic activation leading to tachycardia, vasoconstriction and increased inotropism, in a physiologic attempt to maintain vital organ perfusion [17, 18]. In this phase, high levels of circulating catecholamines are also produced at the level of gut, lymphocyte, macrophages and neutrophils [18]. Despite increased sympathetic outflow, the septic heart is characterized by depressed contractility due to the attenuation of the adrenergic response at the cardiomyocyte level. This impaired adrenergic response is mediated by cytokines and nitric oxide (NO), which cause downregulation of β -adrenergic receptors and depression of post-receptor signaling pathways [18]. Adrenergic response is further blunted by neuronal apoptosis in the cardiovascular autonomic centers and by catecholamine inactivation by reactive oxygen species (ROS) [18]. Because 75–80 % of myocardial adrenergic receptors are β_1 , the attenuation of the adrenergic response represents a major mechanism of sepsis-induced cardiac dysfunction.

In addition to impaired adrenergic response, suppression of L-type calcium currents, decreases in ryanodine receptor density and activity, as well as changes in calcium re-uptake into the sarcoplasmic reticulum have all been demonstrated in experimental sepsis and constitute another cause of septic myocardial dysfunction [18]. Down-regulation of β -adrenergic receptors and altered intracellular calcium trafficking with decreased myofilament responsiveness to calcium are among the main underlying mechanisms of septic myocardial dysfunction but also account

for the attenuated hemodynamic effects of dobutamine infusion in septic shock compared with less severe sepsis and non-septic heart failure [12, 18, 19]. Incremental doses of dobutamine may, therefore, be required to achieve therapeutic goals. Nevertheless, in the presence of elevated endogenous sympathetic outflow, such as in septic shock, incremental doses of dobutamine may dramatically increase the risk of adverse effects and lead to myocardial structural damage [1, 5, 7, 9]. In a state of oxygen delivery and consumption mismatching, such as septic shock, enhancing muscle contraction with dobutamine by increasing intracellular calcium concentration and subsequently myocardial oxygen consumption, may further deteriorate myocardial performance. Not surprisingly, Schmittinger et al. [9] observed histologic lesions indicative of stress-induced cardiotoxicity in most patients dying from septic shock. Furthermore, it has also been demonstrated that catecholaminergic inotropic support in sepsis is among the leading causes of LV apical ballooning in patients admitted to the intensive care unit (ICU) [10].

In the light of these pathological mechanisms, the strong rationale for administration of levosimendan to improve septic myocardial dysfunction is related to the ability of this compound to exert positive inotropic effects independent of interactions with β -adrenergic receptors and cAMP production, thereby leaving intracellular calcium concentrations unaffected [20, 21]. In the cardiac myocyte, levosimendan selectively binds to the N-domain of cardiac troponin C (cTnC), thereby stabilizing the calcium-dependent interaction between cTnC and cTnI. The conformational change in cTnC is an essential condition for the interaction between actin and myosin microfilaments necessary to generate contractile force [20, 21]. Because decreased myofilament responsiveness to calcium is a major determinant of septic myocardial depression, calcium sensitization may be more effective, compared to just increasing intracellular calcium concentrations (e. g., with dobutamine), in counteracting septic myocardial depression [12, 22]. An additional advantage of this mechanism is that in parallel to improving cardiac performance, levosimendan decreases sympathetic activity leading to a reduction in catecholamine concentrations [23]. In the presence of septic myocardial depression, levosimendan may, therefore, improve cardiac performance without promoting tachyarrhythmia or relevant increases in myocardial oxygen consumption [11–16, 18, 20, 21].

Effects on systolic function

Oldner et al. [24] demonstrated a marked improvement in cardiac index (CI) and systemic DO_2 following the administration of levosimendan in an experimental model of sepsis. Nevertheless, in parallel with the increase in CI, the authors observed a decrease in mean arterial pressure (MAP) and systemic vascular resistance index (SVRI). Other studies confirmed these preliminary findings. In isolated guinea pig hearts, incremental concentrations of levosimendan improved systolic function, with positive effects following concentrations $> 0.03 \mu\text{M}$ [25]. An increase in LV contractility was observed in two rabbit endotoxic models with animals receiving levosimendan at doses of 3.0 or 3.3 $\mu\text{g}/\text{kg}/\text{min}$ (with no loading dose) [26, 27]. In a study by Barraud et al. [27], changes were noticed in preload and load independent measurements, thus suggesting a direct increase in contractility inde-

pendent of volume status or changes in vascular properties [21, 27]. Improved cardiac efficiency was indirectly confirmed by the ability of levosimendan to increase systemic DO_2 as well as mixed venous oxygen saturation (SvO_2) [24, 26, 28]. In two recent studies, addition of levosimendan to arginine-vasopressin (AVP) improved global hemodynamics and resulted in a survival benefit compared to AVP infusion alone or placebo in animals with septic shock secondary to generalized peritonitis [29, 30].

In contrast to the experimental models, extensive clinical data on levosimendan to treat septic myocardial depression are still lacking and are mainly restricted to small single center trials with its use described for the first time in a case report in 2005 [11]. Our research group [12] performed the first clinical trial aimed at evaluating the effects of levosimendan in septic shock patients. Patients with septic shock with persistent LV ejection fraction (LVEF) $<45\%$ after 48 h of standard therapy

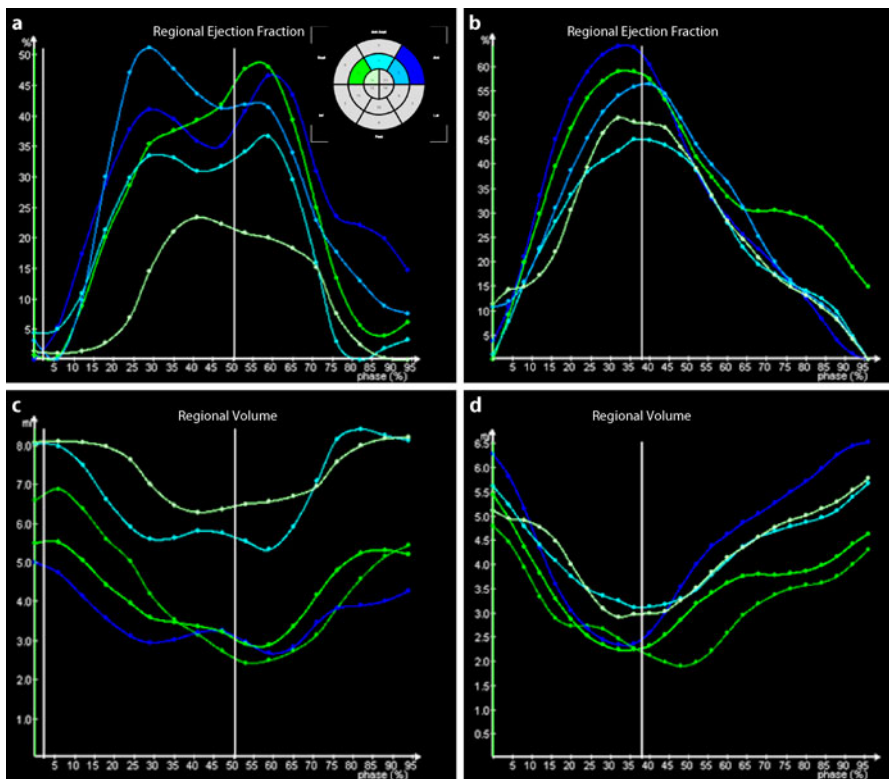


Fig. 2 Regional left ventricular ejection fraction and end diastolic volume. Regional ejection fraction and end-diastolic volume after switching dobutamine $5\ \mu\text{g}/\text{kg}/\text{min}$ (a, c) to levosimendan $0.2\ \mu\text{g}/\text{kg}/\text{min}$ (b, d). The different lines represent different regions of the left ventricle. The figure shows the improvements in regional myocardial kinetics leading to a better cardiac performance following levosimendan infusion

(volume substitution, norepinephrine and dobutamine) were randomized to receive levosimendan (0.2 $\mu\text{g}/\text{kg}/\text{min}$ infusion without preceding bolus) or dobutamine infusion (5 $\mu\text{g}/\text{kg}/\text{min}$) for 24 h. Norepinephrine was titrated to maintain MAP at 70–80 mmHg. In this study, we observed an increase in CI and LVEF following levosimendan infusion. Levosimendan was also superior to dobutamine in improving end-diastolic and end-systolic volume index and LV stroke work index (LVSWI). Although we did not perform a direct evaluation of cardiac contractility, our findings suggest that overall myocardial function was improved (Fig. 2). This assumption is also supported by the observed increases in oxygen delivery and consumption (vs. baseline) and the decrease in arterial lactate (vs. baseline and dobutamine) observed 24 h after levosimendan infusion, indicating an improvement in global tissue oxygenation. Importantly, we did not find a decrease in MAP or an increase in norepinephrine requirements [12]. Although one could anticipate that a higher dose of dobutamine (10, 15, or 20 $\mu\text{g}/\text{kg}/\text{min}$ as suggested by current guidelines) would have produced the same beneficial effects as levosimendan on hemodynamics, the increased risk of adverse effects also needs to be taken into account. An improvement in global hemodynamics following levosimendan infusion was observed by the same group in patients with acute respiratory distress syndrome (ARDS) and septic shock [13] and by Powell and De Keulenaer [14] in a case series of septic shock patients. More recently, Busani et al. [31] reported an increase in myocardial contractility after switching from dobutamine (up to 8 $\mu\text{g}/\text{kg}/\text{min}$) to levosimendan (0.1 $\mu\text{g}/\text{kg}/\text{min}$) in a case of fulminant peri-myocarditis associated with influenza A/H1N1 virus.

Effects on diastolic function

Diastolic dysfunction is strongly associated with age, hypertension, diabetes mellitus, and coronary artery disease. In view of the growing elderly and morbid patient population treated in modern ICUs, the number of septic patients who will suffer from diastolic dysfunction is likely to increase in the future [32]. Patients with septic shock frequently have both systolic and diastolic dysfunction. Whereas patients with systolic dysfunction have better survival and myocardial dysfunction recovers if patients survive the septic course [18], diastolic dysfunction does not improve and is associated with high mortality [33]. Although it is conceivable that diastolic dysfunction is a pre-existing condition in the majority of septic patients [33], one cannot exclude that in these patients diastolic dysfunction can be aggravated not only by the disease *per se* but also by the treatment, especially if echocardiography is not performed. Correct hemodynamic management is crucial to prevent worsening of diastolic dysfunction in septic shock. As a consequence of down-regulation of β -adrenergic receptors, dobutamine loses its lusitropic effect due to hyperphosphorylation of troponin I, a condition that renders the myocytes refractory to further phosphorylation in response to dobutamine [27]. More importantly, dobutamine, by increasing heart rate and inducing tachyarrhythmia, may dramatically worsen diastolic dysfunction. Conversely, levosimendan binds to cTnC in a calcium-dependent manner. It dissociates from cTnC when calcium concentration decreases during diastole, thereby acting only during systole and not impairing diastolic myocardial

relaxation [20, 21]. In addition, since levosimendan causes a significant decrease in sympathetic nervous system activity, its administration is not associated with an increase in heart rate, allowing better ventricular filling during diastole. In this regard, Barraud et al. [27] demonstrated that in contrast to dobutamine, levosimendan produced a parallel enhancement of myocardial contractility and improvement in LV diastolic function in experimental septic shock.

Vasodilation

Levosimendan not only increases myocardial contractility, but also induces arterial and venous vasodilation [20, 21]. Vasodilation is the result of the opening of potassium channels, including K_{ATP} channels in small resistance vessels and Ca^{2+} -activated and voltage-gated K^+ channels in large conductance vessels. This action is linked to hyperpolarization of the membrane with subsequent inhibition of the inward Ca^{2+} current and activation of the Na^+ - Ca^+ exchanger to extrude Ca^{2+} . The resultant decrease in intracellular Ca^{2+} ions then contributes to vasorelaxation [20, 21]. The vasodilatory effect of levosimendan has been demonstrated in several vasculatures including coronary and pulmonary arteries, systemic arteries, and veins [20].

Vasodilation and its effects on cardiac performance

The vasodilatory effects of levosimendan may play a pivotal role in improving cardiac performance in patients with septic myocardial dysfunction. The matching between the ventricle and arterial load is crucial to provide adequate blood flow to the peripheral tissues. A sufficient cardiac output is the net result of various combinations of myocardial contractility (stroke volume) and afterload (systemic vascular resistance) and the cardiovascular system chooses any combination of these to optimize coupling between the ventricle and the arterial system [6, 34]. The maximum efficiency of the cardiovascular system with the lowest energy costs is obtained when the whole pulsating energy produced by the left heart is transmitted downstream to the peripheral regions [6, 34]. Ventriculo-arterial coupling, the ratio between arterial elastance and ventricular elastance, has therefore been recognized as an accurate index of cardiovascular performance. When this ratio is near unity, the efficiency of the system is optimal. In this case, the left ventricle provides an adequate stroke volume with the lowest possible energy consumption [6, 34]. Patients with septic myocardial dysfunction may present some degree of ventriculo-arterial uncoupling, because of an imbalance between increased arterial elastance induced by pharmacological vasoconstriction and decreased ventricular elastance depending on the reduction in myocardial contractility [6]. Ventriculo-arterial uncoupling may, therefore, worsen or contribute to septic myocardial dysfunction. This assumption is supported by an echocardiographic evaluation performed in a series of septic shock patients [35]. Among the 67 patients investigated, 14 patients without global LV hypokinesia at admission, developed the condition after 24 hrs or 48 hrs of continuous norepinephrine infusion. Although this change could have been related to

the progression of the disease, one cannot exclude that increasing LV afterload with norepinephrine impaired ventriculo-arterial coupling, leading to myocardial failure. According to guidelines [2], the secondary LV hypokinesia observed in these patients was corrected by addition of dobutamine to the hemodynamic support [35]. Because dobutamine may restore the ratio between arterial elastance and ventricular elastance by increasing only the latter, the cardiac energetics of such a strategy may be unfavorable, especially if prolonged. Furthermore, frequency potentiation of contractile function is a major mechanism for the increase in myocardial performance thanks to an improvement in ventricular-arterial coupling. Conversely, in the failing heart, such as the septic heart, this positive force-frequency relation is impaired with ventricular-arterial coupling that becomes negatively affected by tachycardia [34]. Therefore, in septic myocardial dysfunction, dobutamine may further worsen ventricular-arterial coupling by inducing tachycardia [6, 34]. By contrast, levosimendan improves ventriculo-arterial coupling by acting on both myocardial and arterial elastance. Due to the enhancement of calcium sensitivity to contractile proteins, this drug also restores the positive force-frequency relation and prevents tachycardia-induced adverse effects on ventricular-arterial coupling [34]. Thus, levosimendan repairs ventriculo-arterial uncoupling better than dobutamine because of greater inotropic effects with less energy expenditure and additional vasodilatory effects [6, 35]. With the same mechanisms, levosimendan, by positively affecting right ventriculo-arterial coupling, improves right ventricular (RV) performance and pulmonary hemodynamics. This effect may be of great importance because patients with septic shock may develop an increase in RV afterload leading to RV dysfunction. In the experimental setting, it has been reported that levosimendan decreased mean pulmonary artery pressure as well as pulmonary vascular resistance, without impairing arterial blood oxygenation [24, 28–30, 36]. In 35 patients with ARDS and septic shock, levosimendan infusion contributed to a decrease in pulmonary vascular resistance. The subsequent reduction in RV afterload was associated with a significant increase in RVEF compared to the control group, suggesting an improvement in RV systolic function also [13]. In harmony with our previous study [12], global hemodynamics were improved following levosimendan infusion [13]. A decrease in pulmonary vascular resistance was also noted in case series from Noto et al. [11] and Powell and De Keulenaer [14].

Vasodilation and its effects on regional hemodynamics

The vasodilatory effects of levosimendan may also be effective in improving regional blood flow. Maintaining adequate splanchnic perfusion, particularly of the gastrointestinal mucosa, is crucial because splanchnic hypoperfusion is implicated in the activation of the inflammatory response and subsequent multiple organ failure [17]. Several vasoactive drugs have been used in an attempt to prevent hepatosplanchnic ischemia and to improve intestinal perfusion. Nevertheless, the efficacy of vasoactive agents in preserving splanchnic blood flow or preventing gastrointestinal mucosal ischemia has not been demonstrated. Levosimendan, by increasing cardiac output and simultaneously redistributing perfusion toward splanchnic regions by its additional vasodilatory activity, might be a prophylactic or therapeutic option

to support the integrity of the gastrointestinal mucosa and to preserve splanchnic perfusion during septic shock. In animal models of septic shock, levosimendan was associated with reduced gut vascular resistance, increased portal venous blood flow, increased splanchnic oxygen delivery and consumption, as well as increased mucosal O₂ saturation and reduced intramucosal partial pressure of carbon dioxide (PiCO₂) [24, 28, 36]. These effects were more pronounced following levosimendan administration when compared with dobutamine [28]. Our research group previously demonstrated that levosimendan compared to dobutamine (5 µg/kg/min) increased gastric mucosal perfusion, decreased the PCO₂ gradient and increased capillary blood flow in patients with septic myocardial depression [12]. In a study by Memiş et al. [37], levosimendan improved liver perfusion to a greater extent than dobutamine (10 µg/kg/min) in a series of septic shock patients. Of note, previous studies [12, 38] reported that levosimendan decreased serum lactate more than dobutamine did, although there was no difference between the two drugs with regard to their effects on central venous oxygen saturation (ScvO₂) [38]. These findings suggest an improvement in regional hemodynamics following levosimendan infusion. On the other hand, Hernandez et al. [39] very recently demonstrated that dobutamine (5 µg/kg/min) failed to improve metabolic, hepatosplanchnic or peripheral perfusion parameters despite inducing a significant increase in systemic hemodynamic variables in septic shock patients without low cardiac output but with persistent hypoperfusion. Kidney dysfunction is common among septic shock patients and may be associated with poor outcome. Levosimendan induces vasodilation, preferentially of the pre-glomerular resistance vessels, increasing both renal blood flow and glomerular filtration rate (GFR) without jeopardizing renal oxygenation [40]. We previously reported that in addition to the effects on gastric mucosal flow, levosimendan increased creatinine clearance and urinary output [12, 40].

Vasodilation and its effects on the microcirculation

Microvascular dysfunction plays a pivotal role in the pathophysiology of septic shock and may occur even in the presence of normal systemic oxygen supply and MAP [15, 17, 41]. In this regard, inotropes have been investigated to improve microcirculatory blood flow in patients with septic shock. De Backer et al. [41] reported that dobutamine improved the microcirculation in a series of septic shock patients. In contrast, in a very recent study, similar dobutamine doses (5 µg/kg/min) failed to improve microcirculatory blood flow [39]. Interestingly, in the study by De Backer et al. [41], the subsequent addition of a topical vasodilator, acetylcholine, completely restored sublingual capillary perfusion, supporting the hypothesis that stronger vasodilatory compounds, such as levosimendan, may be more effective than dobutamine in improving microcirculatory blood flow. The physiological implication is that because of their vasodilatory effects, such compounds may improve microcirculatory blood flow by increasing the driving pressure of blood flow at the entrance of the microcirculation [41]. In line with this assumption, we demonstrated that compared to a standard dose of 5 µg/kg/min of dobutamine, levosimendan at 0.2 µg/kg/min improved microcirculatory blood flow in patients with septic shock [15]. Interestingly, the improvement in microvascular perfusion was

independent of changes in cardiac output. This finding suggests that effects of levosimendan at the level of the endothelium, such as the ability to decrease cytokine synthesis, plasma levels of endothelin-1, intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 [20], may have contributed to the improvement in the microcirculation.

Mitochondria K_{ATP} Channel-opening and Organ Protection

Evidence supports the hypothesis that mitochondrial dysfunction and consequent cellular energetic failure may play a key role in the development of sepsis-related organs failure and thus myocardial dysfunction [17, 42]. The mechanisms of such mitochondrial dysfunction are extremely complex and involve an excessive production of ROS, such as superoxide, peroxynitrite and NO, directly inhibiting activities of the respiratory chain complexes [42]. Compounds that have the ability to open the K_{ATP} channels in the plasma membrane of smooth cells, such as levosimendan, may also act on the K_{ATP} channels located at the level of mitochondria. This latter activity may be particularly relevant, because the stimulation of K^+ flux through mitochondrial K_{ATP} has been demonstrated to maintain cellular energy homeostasis and to protect mitochondria from oxidative injury [20]. In this regard, all available clinical data show an increase in SvO_2 following levosimendan administration, which may be related not only to an improvement in systemic hemodynamics but also to a better energetic substrate utilization by mitochondria. Evidence also suggests that levosimendan exerts antioxidant activity and ischemic preconditioning [20, 43]. Whether levosimendan may protect mitochondria and improve energy failure in the presence of multifactorial damage, such as the septic insult, is still unclear. By performing muscle biopsies in a series of septic shock patients, we found that 24 h levosimendan administration at a dose of $0.2 \mu\text{g}/\text{kg}/\text{min}$ increased antioxidant defense and was able to enhance the protein level of two defective respiratory chain enzymes, complex I and III (unpublished data). These preliminary unpublished data suggest that levosimendan may protect mitochondria from oxidative stress during septic shock and, potentially, confront the bioenergetic defect through stimulation of mitochondrial biogenesis.

Clinically Relevant Adverse Effects

Opening of K_{ATP} channels in response to levosimendan administration typically is associated with significant vasodilation increasing the risk of hypotension. Nevertheless, in the presence of an adequate volume status, the decrease in blood pressure may be limited by a simultaneous increase in cardiac output [21]. In this context, it is especially important to underline that the vasodilatory effects of levosimendan are dose-dependent and most pronounced if a loading bolus is administered. In the presence of septic shock, levosimendan should, therefore, only be given when adequate fluid resuscitation can be assured. Since the majority of patients suffering from

septic myocardial dysfunction do not require an immediate increase in myocardial contractility, it is reasonable to continuously infuse levosimendan without a preceding loading bolus dose [44]. Data from the available clinical studies suggest that in the presence of adequate volume status and maintained perfusion pressure with norepinephrine, use of levosimendan is a safe and effective alternative to increasing dobutamine doses in treating the failing heart of septic shock patients. Notably, levosimendan is the only inotrope that is not associated with increased mortality in patients with septic shock [5]. This finding assumes importance in light of the fact that levosimendan is used rather as a last resort treatment than as a first-line agent. In most cases, levosimendan is administered in shock states refractory to conventional inotropes, in a final attempt to save a patient's life. For many such patients, however, this may be too late to adequately reverse organ failure, as underlined by Bollen Pinto et al. [21].

Conclusion

As an inodilator, levosimendan (at low energy expenditure) may improve cardiac performance in the presence of septic myocardial dysfunction by optimizing the ratio between arterial and myocardial elastance, rather than by increasing myocardial contractility itself. Due to its mechanism of action, levosimendan lowers catecholamine concentrations and thus reduces cardiotoxicity. By its vasodilating properties, levosimendan may improve both cardiac performance and regional hemodynamics. In addition to these hemodynamic properties, non-hemodynamic effects of levosimendan may further contribute to improvements in microvascular blood flow and thus organ perfusion. Moreover, levosimendan has no significant effect on platelets and does not affect blood coagulation [45]. Finally, levosimendan may positively affect several other pathophysiological pathways, such as ischemia-reperfusion injuries, apoptosis, inflammation and oxidative stress, which all contribute to worsen septic myocardial dysfunction. Taking into account these effects, levosimendan seems to be the closest available drug to an ideal vasoactive agent for improving septic myocardial dysfunction. Although extensive clinical data are still lacking, the efficacy of levosimendan in treating septic myocardial dysfunction is strengthened by the evidence of increasing use of this drug by ICU physicians for the hemodynamic management of septic shock [46].

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