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Use of Levosimendan in Intensive Care Unit Settings: An Opinion Paper

Antoine Herpain, MD, PhD, Stefaan Bouchez, MD, PhD,† Massimo Girardis, MD, PhD,‡ Fabio Guarracino, MD, PhD,§ Johann Knotzer, MD, PhD,¶ Bruno Levy, MD, PhD,‖ Tobias Liebregts, MD, PhD,** Piero Pollesello, PhD,†† Sven-Erik Ricksten, MD, PhD,‡‡ Hynek Riha, MD, PhD,§§ Alain Rudiger, MD, PhD,¶¶ and Fabio Sangalli, MD‖‖*

Abstract: Levosimendan is an inodilator that promotes cardiac contractility primarily through calcium sensitization of cardiac troponin C and vasodilatation via opening of adenosine triphosphate–sensitive potassium (K_{ATP}) channels in vascular smooth muscle cells; the drug also exerts organ-protective effects through a similar effect on mitochondrial K_{ATP} channels. This pharmacological profile identifies levosimendan as a drug that may have applications in a wide range of critical illness situations encountered in intensive care unit medicine: hemodynamic support in cardiogenic or septic shock; weaning from mechanical ventilation or from extracorporeal membrane oxygenation; and in the context of cardiorenal syndrome. This review, authored by experts from 9 European countries (Austria, Belgium, Czech republic, Finland, France, Germany, Italy, Sweden, and Switzerland), examines the clinical and experimental data for levosimendan in these situations and concludes that, in most instances, the evidence is encouraging, which is not the case with other cardioactive and vasoactive drugs routinely used in the intensive care unit. The size of the available studies is, however, limited and the data are in need of verification in larger controlled trials. Some proposals are offered for the aims and designs of these additional studies.

Key Words: inodilator, hemodynamic support, cardiogenic shock, septic shock, weaning, mechanical ventilation, extracorporeal membrane oxygenation, cardiorenal syndrome

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From the *Department of Intensive Care, Hôpital Erasme, Brussels, Belgium; †Department of Anesthesiology, University Hospital, Ghent, Belgium; ‡Struttura Complessa di Anestesia 1, Policlinico di Modena, Modena, Italy; §Dipartimento di Anestesia e Terapie Intensive, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; ¶Institut für Anästhesiologie und Intensivmedizin II, Klinikum Wels-Grieskirchen, Wels, Austria; ‖INSERM U 1116, Groupe Choc, Equipe 2, Faculté de Médecine, Vandoeuvre Les Nancy, Nancy, France; **Department of Bone Marrow Transplantation, University of Duisburg-Essen, Essen, Germany; ††Critical Care, Orion Pharma, Espoo, Finland; ‡‡Department of Anesthesiology and Intensive Care, Sahlgrenska Universitetssjukhuset, Gothenburg, Sweden; §§Department of Anesthesiology and Intensive Care Medicine, Institute for Clinical and Experimental Medicine, Prague, Czech Republic; ¶¶Institute of Anaesthesiology, University Hospital Zürich, Zürich, Switzerland; and ‖‖Department of Anaesthesia and Intensive Care Medicine, San Gerardo Hospital, Monza, Italy.

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Reprints: Piero Pollesello, PhD, Critical Care, Orion Pharma, P.O. Box 65, 02101 Espoo, Finland (e-mail: piero.pollesello@orionpharma.com).

THE CALCIUM SENSITIZER LEVOSIMENDAN

Levosimendan is a positive inotropic compound with vasodilatory properties[1] used for the treatment of acute decompensated heart failure (HF) and in cases where the use of an inotropic treatment is considered appropriate.[2] The principal mechanism of levosimendan is the sensitization of troponin C to calcium in cardiac muscle,[3–5] which leads to its unique feature of exerting a positive inotropic effect without increasing myocardial oxygen consumption.[6–10] In addition, levosimendan opens adenosine triphosphate–sensitive potassium (K_{ATP}) channels in vascular smooth muscle cells[11,12] and induces vasodilation of the pulmonary,[13] coronary,[14,15] and peripheral arteries[16] and of the venous circulation.[17] By addressing both cardiac inotropy and vascular dilatation, levosimendan improves cardiovascular coupling and cardiac mechanical efficiency. Levosimendan also opens mitochondrial K_{ATP} channels[18] and exerts an organ-protective and, especially, cardioprotective effect in various settings.[19,20] At higher doses, the drug also acts as a phosphodiesterase type 3 (PDE3) inhibitor.[1,12,21,22] The effects of levosimendan are not impaired by the concomitant use of beta-blockers.[23]

Levosimendan has been studied in several therapeutic applications, particularly in the management of acute HF (AHF) patients with low cardiac output[24,25] and in high-risk cardiac surgery.[26,27] Levosimendan has also shown preliminary positive effects in a range of other conditions requiring inotropic support, including right ventricular failure, cardiogenic shock (CS), septic shock, and Takotsubo cardiomyopathy.[28]

Owing to its pharmacology, it has become apparent that levosimendan may also have applications in the setting of intensive care medicine. The conceptual framework for this wider use of levosimendan has been set out by Farmakis et al[28] and is supported by an array of experimental and observational research[29–37] (Box 1).

BOX 1.

Expected Effects of Levosimendan in Intensive Care Unit Settings

- General hemodynamic support;
- Increased ejection fraction and cardiac index without increase of oxygen consumption;
- Peripheral vasodilation and reduction of tissues and organ hypoperfusion;
- Increased GFR and renal function;
- Decrease in need for catecholamines;
- Sustained effects; and
- No increase in long-term mortality.

This commentary identifies a range of clinical situations encountered in the intensive care unit (ICU) where levosimendan may offer clinical advantages, either as an adjunct to standard-of-care therapies or as an alternative to conventional therapies (Box 2).

HEMODYNAMIC SUPPORT IN CARDIAC CRITICAL CARE

In severe AHF and CS, congestion and hypoperfusion lead to a systemic disorder that potentially affects all vital organs. Restoring adequate cardiac output and organ perfusion, and promoting decongestion, are therefore medical priorities during the early phase of treatment.[38–40]

In AHF leading to tissue hypoperfusion, initial use of an inotrope is advocated.[40,41]Hence, inotropic support remains a cornerstone of AHF management in these critically ill patients, together with adequate fluid resuscitation (or depletion) and optimization of arterial pressure to suit the individual features of patients.

Reported rates of inotropic support in AHF management vary from 9% in an early US registry[42] to >30% in a later international registry[43] and 13% in the 2017 European Society of Cardiology (ESC) Heart Failure Long-Term Registry.[44] Robust secular trends in the use of inotropes are hard to identify from these fluctuations but dobutamine remains the most frequently used inotrope.

BOX 2.

Intensive Care Unit Settings in Which the Use of Levosimendan Has Been Described

- Cardiogenic shock;
- Septic shock;
- Weaning from ventilator;
- Weaning from extracorporeal membrane oxygenation;
- Pulmonary hypertension and right ventricular dysfunction; and
- Need for hemodynamic support in patients with diuretic resistance.

The indication for inotropic support depends largely on the etiology; heading this hierarchy is CS, for which, by definition, virtually all patients are supported by at least one inotropic drug.[45] In septic shock, inotropic support is deployed according to current precepts of early goal-directed therapy (EGDT); in recent EGDT trials, rates of inotrope use ranged from ≈15% for patients included in the intervention groups to usually <5% for those in the standard-of-care groups.[46] The prevalence of inotropic support at admission was 15%–20% in a recent pragmatic multicenter trial of levosimendan in septic shock.[37] Inotropic support may also be considered in cases of obstructive shock, while waiting for the obstruction to be removed, but continuation after that point would be uncommon.

Dobutamine is the first-line inotropic agent for resuscitating patients suffering from either severe AHF and low-cardiac output syndrome[40] in CS[41,47] or septic shock[48] but its administration entails substantial addition of exogenous catecholamines to the endogenous ones already overproduced by the intense activation of the sympathetic autonomous nervous system.

The resulting exacerbation of the beta-adrenergic pathway induces an increase in myocardial oxygen consumption via chronotropic and inotropic effects.[49] This catecholamine-induced myocardial oxygenation imbalance exacerbates myocardial ischemia,[50,51] especially at the level of the subendocardium.[52] Inter alia, excessive adrenergic stimulation is also established as a key factor in the pathophysiology of Takotsubo cardiomyopathy[53] and contributes substantially to some manifestations of the septic cardiomyopathies.[54]

Various large international registries relating to AHF and CS have documented higher rates of morbidity and mortality in patients treated with adrenergic inotropes than in severity-matched peers who did not receive catecholamines[42–45]; a recent meta-analysis of randomized clinical trials of dobutamine to treat severe (acute or chronic) HF likewise indicated an increased risk of mortality.[55] These observations, with others,[56] are the basis of the European Society of Intensive Care Medicine AHF/CS guidance that "The use of these [inotropic/vasopressor] agents should, however, be restricted to the shortest possible duration and lowest possible dose to maintain perfusion pressure"[57] and the declaration in the ESC HF guidelines that "There is long-standing concern that [inotropes, especially those with adrenergic mechanisms] may increase mortality."[40]

In a randomized clinical trial involving patients with acutely exacerbated chronic HF, the PDE3 inhibitor milrinone was shown to increase mortality in patients suffering from ischemic cardiomyopathy[58]: a similar finding was also reported in a recent large retrospective cohort study of intraoperative inotropic support in cardiac surgery.[59] These data indicate that milrinone (and, by extension, other PDE3 inhibitors) is not a fully satisfactory alternative to dobutamine. Similar reservations apply to dopamine[44,60] and epinephrine.[45,61]

The "decatecholaminization" of the critically ill patient represents a new and still-evolving paradigm in the treatment of patients in the ICU.[62,63] One avenue for research in this

area has been the evaluation of nonadrenergic vasoactive agents.[64–66] These include levosimendan, which offers positive cardiovascular effects (ventriculoarterial recoupling, decongestion, and cardiac protection against ischemia–reperfusion injury) as well as potentially advantageous ancillary effects on kidney function and diaphragm muscular fibers, as discussed later in this review.

LEVOSIMENDAN IN CARDIOGENIC SHOCK

Acute myocardial infarction (AMI) is the most common etiology of CS but CS may arise from any situation of acute, severe dysfunction in either ventricle of the heart. CS is relatively rare but often fatal.[67]

The standard of care in CS consists of primary percutaneous coronary intervention for AMI, fluid therapy, vasopressors, inotropes and, in the last resort, mechanical assistance.[68] Data from initial comparator studies indicate that levosimendan may be a useful addition to this regimen.

Levosimendan may be a constructive alternative to conventional inotropes for the management of CS. In a trial of 22 consecutive AMI patients who developed CS after percutaneous coronary intervention, levosimendan (24 μg/kg bolus, then 0.1 μg/kg/min for 24 hours) attained the study end point of ≥30% increase in cardiac power output (CPO) consistently better than dobutamine (initial dose 5 μg/kg/min, with subsequent dose increases to reach the desired hemodynamic effect), despite a comparable reduction in pulmonary capillary wedge pressure[69] (Fig. 1) (CPO is the product of cardiac output and mean arterial pressure [MAP] and an indicator of cardiac contractility and ventricular–vascular coupling: in effect, it represents the pumping power of the heart and has been identified as the strongest predictor of survival in patients with CS[70]).

Levosimendan also compared favorably with the PDE inhibitor enoximone in an exploratory open-label study of CS secondary to AMI, giving a small but significant advantage in death from multiorgan failure ($P \approx 0.02$).[71] Beneficial hemodynamic effects were recorded in both groups, including enhancement of CPO, but these changes were achieved sooner with levosimendan than with enoximone. There was a significant advantage with levosimendan in terms of fewer deaths from multiorgan failure ($P < 0.05$). Use of dobutamine and norepinephrine in the levosimendan-treated patients was much lower than that in the enoximone group. It is plausible that part of the survival advantage seen with levosimendan may be attributable to a reduction in exposure to exogenous catecholamines.

Notwithstanding these data, levosimendan is currently regarded as a salvage therapy in CS after dobutamine failure and before extracorporeal life support (ECLS). Any revision of this status will require well-designed randomized controlled studies.[72] Until then, the use of levosimendan may be considered in cases of low cardiac output associated with signs of hypoperfusion or deteriorating renal/liver function, especially if beta-blocker use is part of the clinical scenario.

Use of levosimendan is contraindicated in hypovolemia, which must be excluded using echocardiography and/or advanced monitoring and dynamic indices. Cardiac output monitoring (transpulmonary thermodilution or pulmonary artery catheterization in cases of associated right ventricular dysfunction) is highly recommended.

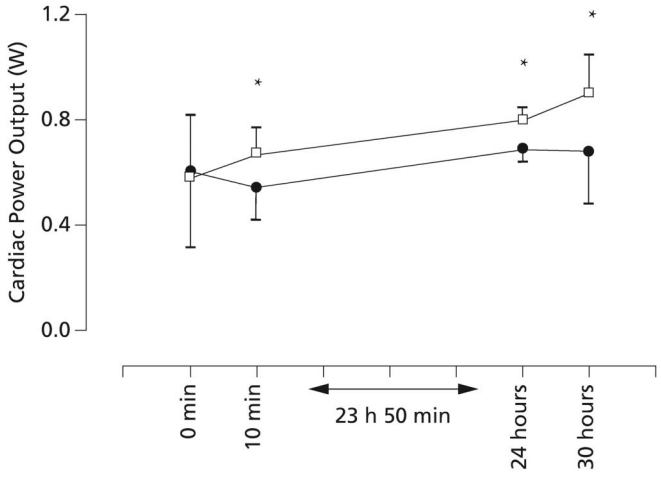

FIGURE 1. Changes in CPO during infusion of levosimendan (□) and dobutamine (●) in patients with AMI revascularized by percutaneous coronary intervention and who developed cardiac shock. Data points are mean ± SD. *$P < 0.05$ (Student's *t*-test). Data from the study by García-González et al.[69]

Omitting a loading dose seems a rationale choice, while the maintenance infusion for a total duration of 24 hours (0.05–0.2 μg/kg/min) should be individually adjusted. After levosimendan is started, dobutamine may be weaned according to the hemodynamic and clinical response (generally after 2 hours). As soon as possible, but after weaning of vasopressors, established chronic HF treatments should be (re-)introduced.

In practice, systolic dysfunction and diastolic dysfunction often coexist. The management of circulatory failure related to diastolic dysfunction in critical illness is largely supportive. Adequate fluid resuscitation is often followed by the administration of drugs with a positive lusitropic effect. Levosimendan has been shown to improve diastolic function[73] and filling and, importantly, it can be safely combined with beta-blockers, which represent one of the potential treatment modalities for diastolic dysfunction.

LEVOSIMENDAN IN SEPTIC SHOCK

Sepsis is defined nowadays as an infection inducing dysfunction of at least one organ owing to a deregulated host inflammatory response.[74] In addition to intrinsic distributive shock due to vascular hyporeactivity and autonomic dysfunction, sepsis can also induce septic cardiomyopathy (SCM) with de novo AHF due to myocardial depression. Such complications contribute to a sepsis mortality rate of ≈30%.[74,75] The prevalence of SCM among septic patients varies widely (from 20% to 60%), a state of affairs that reflects both the current lack of a common definition and the heterogeneity of the symptoms.[75]

Inotropic support is endorsed for restoration of an adequate cardiac output and peripheral oxygen delivery.[48] In

the absence of a fully evidence-based alternative, dobutamine remains the suggested first-line inotrope for those goals, despite the observations that: (1) high levels of circulating catecholamines and adrenergic overstimulation contribute to the pathophysiology of SCM[54,76]; (2) the adrenergic response at the cardiomyocyte level is attenuated by downregulation of β-adrenergic receptors[77,78]; (3) adrenergic drugs have been associated with worse outcomes in a pooled network meta-analysis[36]; and (4) esmolol, a β_1-receptor antagonist, seems to improve the outcome of severe SCM,[78] especially in cases of persistent tachycardia.[79]

Proceeding from the above points, assessment of levosimendan as an alternative inotropic drug in septic shock should address the following clinical goals and criteria.

1. Dobutamine sparing: reducing the high (toxic) levels of endogenous and pharmacological adrenergic stimulation and hence restoring a better myocardial oxygenation balance, particularly in the case of coronary artery disease with potential catecholamine-induced ischemia.[51]
2. Attenuation of multiple-organ failure (MOF): reducing the occurrence and/or severity of sepsis-induced MOF due to better regional blood flow distribution in addition to a global increase in cardiac output, plus pleiotropic effects at the cellular and mitochondrial levels.[28,80]
3. Inotropic rescue therapy: restoring inotropic responsiveness in cases of severely attenuated adrenergic response.
4. Drug safety: replacing adrenergic inotropic drugs without tachyarrhythmia or any additional requirement for vasopressors.

Experimental studies (mainly in animal models of peritonitis-induced septic shock) have demonstrated an improvement in survival, and a reduction in the severity of MOF and anti-inflammatory protective effects with levosimendan.[80,81] It must be acknowledged, however, that many of those studies were restricted to comparison versus placebo, not other inotropes.

As regards clinical trials of levosimendan in septic shock, in a monocentric randomized controlled trial, a 24-hour infusion of levosimendan (0.2 μg/kg/min) was compared with dobutamine (5 μg/kg/min) as inotropic support for patients with de novo severe SCM (n = 28) and a left ventricular ejection fraction (LVEF) <45% despite 48 hours of conventional standard-of-care treatment, including dobutamine.[82] Levosimendan use was associated with increases in cardiac output and pulmonary decongestion, without an increase in vasopressor requirements (owing to volume expansion) and with more favorable evolution of various MOF surrogates (lactate clearance, venoarterial carbon dioxide gap, gut mucosal perfusion, and renal function). Dobutamine did not materially alter any of these systemic or regional hemodynamic variables.

The findings of this study satisfy the clinical goals identified above and are, to that extent, promising regarding the potential of levosimendan in sepsis and SCM. However, this was a single study with several limitations and must be considered indicative, not definitive.[83]

The biological mechanisms underpinning this attenuation of MOF have been explored in subsequent clinical trials: levosimendan infusion has been shown to improve microcirculation perfusion,[84] relieve mitochondrial oxidative stress,[85] and restore the muscular lactate/pyruvate ratio.[86] Some of this research, plus additional small clinical trials of heterogeneous quality, has been incorporated into a meta-analysis[87] of the effects of levosimendan in septic shock versus standard inotropes (invariably dobutamine where specified). Findings from this exercise (7 studies, 249 patients) included a significant reduction in mortality in the levosimendan group without intergroup differences in MAP or norepinephrine usage.

These clinical observations, together with a strong experimental background, led to the development of a large pragmatic multicenter randomized placebo-controlled trial of levosimendan in sepsis. This study—Levosimendan for the Prevention of Acute oRgan Dysfunction in Sepsis (LeoPARDS; ISRCTN12776039)—examined whether early administration of levosimendan (0.05–0.2 μg/kg/min for 24 hours) could avert the onset of MOF in a broad population of septic shock patients (n = 516) fulfilling the criteria for systemic inflammatory response syndrome due to infection and requiring vasopressor therapy for at least 4 hours.[37]

LeoPARDS did not fulfill the primary end point of a significant intergroup difference in mean daily Sequential Organ Failure Assessment score favoring levosimendan, and nor was mortality reduced. Although prima facie disappointing, these findings should be considered in perspective. This was a relatively low-risk cohort; most patients were not suffering from either severe circulatory shock or severe SCM needing inotropic support. Moreover, the degree of renal replacement therapy already being undertaken before randomization was substantial and may have led to faster elimination of the study drug in 17% of patients in the intervention group. These reasons may have resulted in LeoPARDS lacking the necessary focus to identify an effect of levosimendan on the patients who could have benefitted.

The currently available clinical evidence in septic shock indicates that: (1) Levosimendan can successfully replace dobutamine in supporting severe de novo AHF due to SCM, with additional positive extracardiac effects owing to amelioration of MOF. These results need to be replicated on a larger scale; and (2) Indiscriminate use of levosimendan (ie, without selecting severe cases of cardiovascular failure) to prevent the development of MOF is safe from a hemodynamic perspective but may confer no clinical benefit.

In addition, however, recent data from patients in septic shock show ventriculoarterial uncoupling due to either ventricular elastance reduction (as in SCM) or increased arterial elastance due to vasopressor therapy, or both: this is a situation in which cardiac mitochondrial function can be severely impaired and the oxygen metabolism altered.[88] No data are currently published on the effect of levosimendan on ventriculoarterial coupling in septic shock, but this matter merits research because the mechanism of action of levosimendan may contribute to the restoration of more normal coupling.

Future investigations to refine the role of levosimendan in the management of septic shock should address (1) the severity of AHF (a priori, there is a case for reserving levosimendan for patients more likely to benefit from it, such as those with severely reduced LVEF or significant coronary artery disease[26,89]); and (2) the timing of the administration (under which heading, matters for attention include investigation of levosimendan as a first-use inotrope for severe SCM to optimize its positive cardioprotective effects as intimated from various lines of research, including randomized trials in cardiac surgery that recorded better outcomes with earlier administration[89–92]).

LEVOSIMENDAN AND WEANING FROM THE VENTILATOR

About 10%–20% of intubated patients in ICUs are difficult to wean from mechanical ventilation, resulting in increased morbidity, mortality, and health care costs.[93,94] Part of this phenomenon may be attributable to the development of diaphragm weakness in intubated patients. Mechanical ventilation results in rapid loss of diaphragmatic force production.[95–97] In one recent study, half of the patients (n = 185) with diaphragmatic dysfunction failed weaning, half of whom died.[98] In addition, liberation from mechanical ventilation to spontaneous ventilation may dramatically increase left ventricular filling pressure and pulmonary artery pressure, especially in patients with preexisting cardiac and/or pulmonary comorbidities.

The pathophysiology of muscle weakness in these patients is complex[99,100] but includes muscle fiber atrophy and reduced calcium sensitivity of the contractile proteins.[101] Because respiratory muscle troponin resembles cardiac troponin, it is plausible that levosimendan may enhance muscular contractility in the same way that it enhances cardiac contractility. This supposition has support from in vitro data,[102] experimental research,[103] and a healthy volunteer study.[104] Positive effects were seen in both slow and rapid diaphragm muscle fibers.[102,103]

Levosimendan has been compared with dobutamine in difficult-to-wean chronic obstructive pulmonary disease patients.[105] Levosimendan resulted in significantly greater inhibition of spontaneous ventilation-induced congestion caused by a rapid increase in pulmonary artery occlusion pressure. Similarly, mean pulmonary artery pressure increased to a lesser extent with levosimendan than with dobutamine. In a prospective observational study in ventilator-dependent difficult-to-wean ICU patients with diminished LVEF (<40%), levosimendan improved cardiac contractility and oxygenation variables and increased the likelihood of separation from mechanical ventilation.[93] A study entitled "Effects of Levosimendan on Diaphragm Function in Mechanically Ventilated Patients" (NCT01721434) coordinated by the University Medical Center, Nijmegen, the Netherlands, is currently recruiting.

LEVOSIMENDAN AND WEANING FROM EXTRACORPOREAL MEMBRANE OXYGENATION

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is increasingly used for short-term management of refractory CS caused by AMI, myocarditis, cardiac surgical procedures in high-risk patients with reduced LVEF, refractory cardiac arrest, and other conditions. In general, it is reserved for situations where pharmacological support of the circulation is not able to restore adequate cardiac output. In cases where there is sufficient recovery of myocardial function during VA-ECMO support, the phase of weaning starts by reducing blood flow through VA-ECMO and thus increasing blood flow to the native heart chambers and pulmonary circulation, ie, increasing the load imposed on both ventricles. In a large observational study, the rate of successful weaning in 4658 patients with CS was reported to be limited to 65.7%.[106]

A first report on levosimendan in the context of VA-ECMO weaning showed that pretreatment 24 hours before the start of weaning was associated with a 50% reduction in the need for inotropic and/or vasopressor support during or after weaning, compared with a 100% requirement in the retrospective control group (n = 11) ($P < 0.003$).[107] The weaning success rate was significantly higher with levosimendan (83.3% vs. 27.3%; $P = 0.0498$); the difference in survival rate was substantial but not statistically significant (66.6% vs. 36.4%).

In a recent retrospective analysis of 240 patients on VA-ECMO after cardiovascular surgery, levosimendan was given during the first 24 hours of ECMO support in 74.6% of cases.[108] The adjusted hazard ratio for failure of ECMO weaning with levosimendan was significantly improved versus control (hazard ratio 0.41; 95% confidence interval 0.22–0.80; $P = 0.008$); furthermore, patients in the levosimendan group experienced lower 30-day mortality ($P = 0.016$) and better long-term survival (Fig. 2). Another study reported improvement in endothelial function after levosimendan infusion in the patients on VA-ECMO, together with an improvement in cardiac function (ie, an increase in cardiac output), facilitating weaning from ECMO.[109] Very recent data show that levosimendan enables weaning from ECLS without increasing norepinephrine requirements when compared with a control group receiving milrinone.[110]

Most patients require inotropic drugs to support myocardial contractile function during weaning from VA-ECMO, and the limited clinical evidence currently available suggests that levosimendan offers some important advantages over other inotropes for this vulnerable period: no increase in myocardial oxygen consumption, a prolonged cardiovascular effect (days), and improvement in endothelial function.

LEVOSIMENDAN IN PULMONARY HYPERTENSION AND RIGHT VENTRICULAR DYSFUNCTION

Acute postoperative pulmonary hypertension is a rare but serious event after weaning from cardiopulmonary bypass and must be managed aggressively to avoid right ventricular failure.[111,112] The in-hospital mortality rate is high and may reach 70%–75%.[113,114] Similar considerations apply in nonsurgical ICUs where right ventricular dysfunction may emerge as a complication of acute respiratory distress syndrome.[115]

The thin-walled right ventricle has poor tolerance for acute increases in afterload. Ventricular distension leads to severe compromise of contractility concomitant with an increase in oxygen consumption. Ventricular interdependence then implicates the left ventricle, leading to reduced filling,

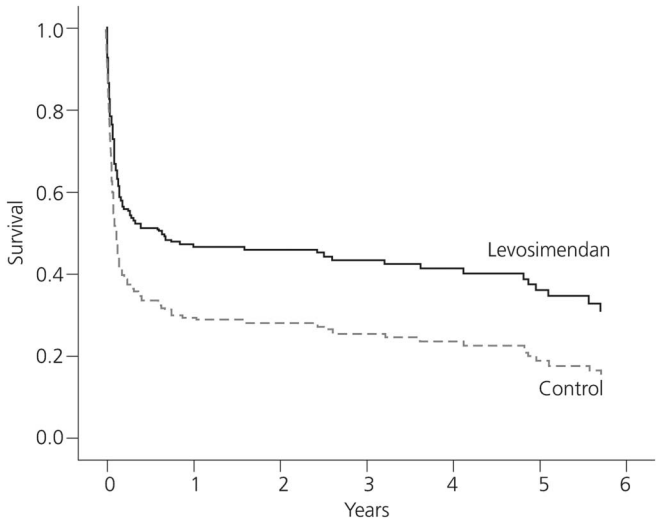

FIGURE 2. Confounder-adjusted long-term survival (levosimendan vs. control, $P = 0.04$) in 240 patients weaned from extracorporeal membrane oxygenation. Levosimendan was administered within the first 24 hours after initiation of ECMO therapy, at a standard dose of 12.5 mg in 24 hours. Data from the study by Distelmaier et al.[108]

decreased cardiac output and oxygen delivery, and decline in systemic perfusion pressure.[116] The pressure gradient for the perfusion of the right coronary artery drops as aortic pressure decreases and right ventricular pressure increases, leading to right ventricular ischemia.[117]

Augmentation of right ventricular function with inotropic support is central to counteracting this vicious cycle. Levosimendan improves myocardial contractility, with a reduction in pulmonary vascular resistance.[118] In an experimental pressure load–induced model of right ventricular failure, levosimendan improved right ventricular to pulmonary artery coupling more than dobutamine.[119] The treatment of acute right ventricular failure involves reversing the cause of the increased pulmonary vascular resistance while maintaining adequate MAP. To support adequate systemic arterial tone, a vasopressor is often required, while levosimendan helps to decrease pulmonary vascular resistance and filling pressures.

Investigator-initiated studies have been performed in patients with right ventricular failure. In these, levosimendan reduced increased right ventricular afterload and improved right ventricular contractility and diastolic function.[120–123]

A recent meta-analysis demonstrated that levosimendan decreased systolic pulmonary pressure and pulmonary vascular resistance concomitant with an increase in right ventricular ejection fraction in patients suffering from acute right HF.[124] Much of the extant data come from noncardiac surgery patients suffering from the acute onset of pulmonary hypertension and/or right ventricular dysfunction; data on levosimendan in acute right ventricular failure are sparse though encouraging.[125]

LEVOSIMENDAN AND RENAL FUNCTION

Evidence for a renal-protective action of levosimendan in preclinical experiments is persuasive but the clinical data set supporting a renal-protective effect rests on a limited number of studies, many of which are small and characterized by heterogeneities.[126] The results of those studies acquire significance only when pooled in meta-analyses[127–130] but, addressed in that way, the findings are suggestive of a renal-protective effect of levosimendan in a range of cardiac low-output states that may be pertinent to the ICU setting.

Levosimendan has been compared with dobutamine in 88 patients with HF who required inotropic therapy.[131] Calculated glomerular filtration rate (GFR) improved in response to levosimendan (0.1–0.2 μg/kg/min, with loading dose at the discretion of individual physicians) but was unchanged in patients who received dobutamine (5 μg/kg/min for at least 6 hours, with subsequent dose alteration or extension beyond 24 hours as judged necessary in individual cases). Complementary findings emerged from a placebo-controlled study in 66 patients hospitalized for decompensated HF and renal dysfunction, with a statistically significant improvement in calculated GFR in patients who received levosimendan (12 μg/kg optional loading dose, then continuous infusion at 0.05–0.2 μg/kg/min for 24 hours). Peak effect was attained 3 days after a 24-hour infusion and the effects persisted for up to 14 days.[132] Two open-label studies also reported reduction of serum creatinine levels in levosimendan-treated patients.[133,134] In a recent randomized study[135] on the effect of levosimendan on renal outcome in 90 cardiac surgery patients with chronic kidney disease and perioperative cardiovascular dysfunction, the authors reported a significant reduction in postoperative acute kidney injury (AKI) and a lower incidence of major complications in the levosimendan arm.

What are the mechanisms behind the clinical observation that levosimendan seems to improve renal function in patients with AHF requiring inotropic support? Inodilators increase cardiac output and also potentially renal blood flow (RBF). It is not immediately evident, however, that an inodilator with renal vasodilating properties also increases GFR: it depends on its effect on the longitudinal distribution of renal vascular resistance. Thus, theoretically, an inodilator that dilates the preglomerular resistance vessels (afferent arterioles) will, at a certain MAP, increase both RBF and GFR. However, an inodilator that preferentially causes vasodilation of the postglomerular resistance vessels (efferent arterioles) will increase RBF but cause a fall in GFR, due to a fall in the upstream glomerular hydraulic pressure. Finally, an inodilator that dilates both preglomerular and postglomerular resistance vessels will induce a pronounced increase in RBF with no change in GFR. Redfors et al[136] showed in postcardiac surgery patients that low-dose dopamine (2–4 μg/kg/min) induced a pronounced 40%–50% increase in RBF with no effect on GFR, suggesting vasodilation of both preglomerular and postglomerular resistance vessels. Levosimendan, however, has been shown to increase both RBF and GFR after cardiac surgery, indicating that, in contrast to dopamine, levosimendan improves renal performance by means of preferential preglomerular vasodilation[137] (Fig. 3). The major goal in the treatment of AKI is to increase GFR. There is, however, a close association between GFR and renal oxygen consumption[138] because any agent that increases GFR will also increase renal oxygen demand. Thus, an ideal inodilator

to treat AKI would be one that increases both RBF and GFR. Such an agent will not only increase GFR but will also meet the increased renal metabolic demand by means of increased renal oxygen delivery. Bragadottir et al[137] showed that the levosimendan-induced increase in GFR did not impair the renal oxygen supply/demand relationship, suggesting that levosimendan could be an interesting agent for treatment of AHF accompanied by impaired renal function in various clinical settings. In a recent double-blind randomized clinical trial, the same group recently showed that in patients with chronic HF and renal impairment, levosimendan increases GFR to a greater extent than dobutamine and thus may be the preferred inotropic agent for treating patients with cardiorenal syndrome.[139]

Complementary findings were reported from a placebo-controlled study by Fedele et al[140] in patients with acute decompensated HF and moderate renal impairment (NCT00527059). Yilmaz et al[126] have speculated on the likely contribution of K_{ATP} channel-opening effects of levosimendan in vascular smooth muscle to a direct renal-protective effect of levosimendan separate from, and additional to, its effects through improved cardiac function and systemic hemodynamics. Observations on the significance of levosimendan-mediated vasodilatation and decongestion have been made by Damman and Voors.[141]

Diuretic resistance in HF patients is a common problem. One treatment option could be the administration of levosimendan. This might be a good option before the more aggressive implementation of ultrafiltration.[142]

OTHER SETTINGS

Is to be noticed that the HFA-ESC Task Force on Takotsubo syndrome[143] advocates levosimendan as the single form of inotropic support in cases of unavailable ECLS. Case reports are encouraging,[144] and the pathophysiology is conceptually a good fit to the properties of levosimendan.

CONCLUSIONS

Levosimendan has been demonstrated to have potential utility in a range of critical illness scenarios. It must be acknowledged, however, that in each sphere of application, the evidence is incomplete or indicative rather than conclusive, and further clinical evaluation will be needed to substantiate the case for levosimendan and to refine the patient categories and dosage schedules likely to be associated with the greatest clinical benefit.

Having levosimendan a vasodilatory effect, its dosage should be guided in part by following the blood pressure of the patient (as recommended by the indication for use), with bolus omitted or used only if SBP is ≥100 mm Hg[145] (Box 3). Meta-analysis of 45 randomized controlled trials in cardiac surgery or cardiology identifies an infusion rate range of 0.05–0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$, with some indications that both lower rates (≤ 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and omission of bolus dose may confer greater long-term survival advantages over higher doses and use of bolus.[146] The presence of a long-lived metabolite is associated with the persistence of the hemodynamic effects of levosimendan[147] for 7–10 days after a single 24-hour infusion of levosimendan. The inodilator levosimendan is mainly used for its hemodynamic effects, and the longer action of its active metabolite is fully consistent with the pharmacologic effects observed in the beginning of the treatment: no increase in the rate of adverse events was observed after the 24-hour infusion of levosimendan.[148]

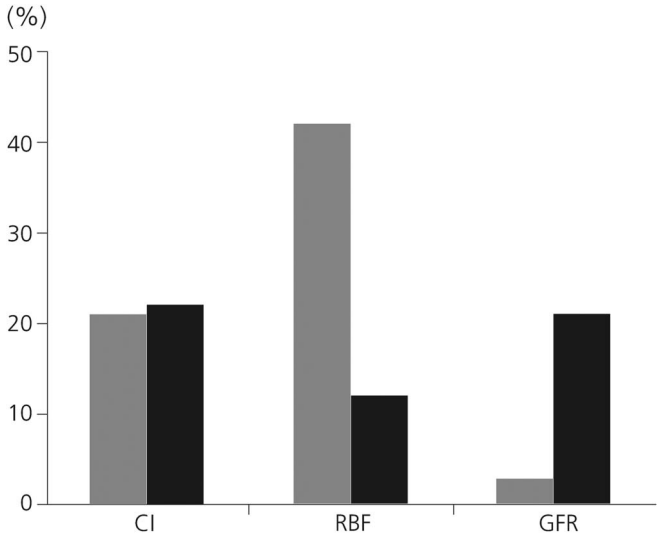

FIGURE 3. Differential effects of levosimendan (0.1 μg/kg/min) and dopamine (2 μg/kg/min) on RBF and GFR in 30 post-cardiac surgery patients. The experimental procedure started 4–6 hours after surgery in the ICU during propofol sedation and mechanical ventilation. Cardiac index (CI) was increased by ≈20% by both drugs. Data from the study by Bragadottir et al.[137]

BOX 3.

Recommended Dosage of Levosimendan When Used in Intensive Care Unit Settings

- Levosimendan dosage should be guided by following the blood pressure;
- Bolus should be omitted or used only if SBP is ≥100 mm Hg;
- An infusion rate range of 0.05–0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ starting at 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and uptitrated or downtitrated to the doses, which gives hemodynamic stability while avoiding adverse effects such hypotension and/or arrhythmias;
- Hypovolemia and hypokalemia should be avoided before and during treatment;
- The presence of a long-lived metabolite is associated with the persistence of the hemodynamic effects of levosimendan 7–10 days after a single 24-hour infusion of levosimendan;
- Levosimendan is mainly used for its hemodynamic effects, and the longer action of its active metabolite is fully consistent with the pharmacologic effects observed in the beginning of the treatment: no increase in the rate of adverse events (hypotension and/or arrhythmia) is observed after the 24-hour infusion of levosimendan.

The regulatory Phase IIb–III clinical trials program on the efficacy and safety of levosimendan in AHF completed in 2005 (see complete trial list in the study by Pollesello et al[149]) did not give an unequivocal answer to the question whether the short-term use of levosimendan lowers long-term mortality in patients hospitalized for decompensated AHF irrespectively to its etiology and to the use of comedications during the preacute, periacute, and postacute phase. Some trials showed a significant improvement in survival, whereas some (the larger ones) did not, but the bulk of evidence did overall support the efficacy and safety of the drug, and a market authorization was granted in over 60 countries, with the notable exception of the United States and the United Kingdom. The regulatory studies included a broad variety of patients, both as it regards the etiologies of AHF (eg, de novo vs. chronic decompensated), the monitoring (eg, invasively vs. non-invasively), the time of treatment (eg, early during hospitalization vs. late), and the co-medications (eg, beta-blockade vs. non–beta-blockade). When more homogeneous groups of patients are considered (see the analysis by Kivikko et al[91]), the short-term effects of levosimendan on symptoms, hemodynamics, and neurohormones are accompanied to a significant long-term effect on survival. As it regards the clinical studies in the ICU field, the same pattern can be seen when comparing the large LeoPARDS study[37] with the many previous smaller studies on the use of levosimendan in septic shock[150]: when the patients are poorly defined, the results are so spread that not any statistical significance can be reached. Therefrom originates the conundrum: in the field of ICU, the large studies needed for "evidence-based medicine" necessarily include a broad spectrum of patients and the effects of drugs can be easily masked in the statistical analyses, whereas smaller (often monocentric) studies can spot significant positive drug effects due to the more homogeneous selection of patients, but their results will remain necessarily limited. We hereby propose possible solutions for a way out.

Central to future investigations must be the identification of robust and relevant end points. An improvement in survival/mortality may be plausible in cases where levosimendan substitutes for an adrenergic inotrope with a documented propensity to increase mortality. In other settings, however, it is not obvious that a mortality gain can be assumed nor is it certain that any such gain, welcome as it would be, would be the most pertinent measurement of any treatment effect. It is, moreover, unclear how far into the future any survival benefit from a short-term intervention in what is likely to be a complex and multifaceted medical crisis should reasonably be expected to extend. None of the conventional adrenergic inotropic drugs have in fact been associated with improvements in hard end points such as mortality, and there are many indications to the contrary. The reported experience of Distelmaier et al[108] (Fig. 2) is encouraging regarding the prospect of a long-term advantage in the sphere of weaning from ECMO but may not be similarly applicable in other situations and is in any case in need of corroboration.

We consider, for these reasons, that an overemphasis on crude mortality may not be the most informative approach to future clinical trials of levosimendan. We are inclined toward the position of Schumann et al,[72] who have advocated the evaluation of EGDT in CS and low-cardiac output syndrome, arguing that refining the best therapeutic strategy is more constructive than trying to identify the "best" drug for hemodynamic support. Similarly, identifying the most effective regimen for, say, weaning from ECMO or the management of pulmonary hypertension needs to take a wider view of the issue than simply focusing too closely on the impact of a single intervention, perhaps delivered for a short period. The adoption of hierarchical end points in clinical trials of levosimendan in HF (eg, LEODOR; NCT03437226)[151] is an innovation that may also find applications in future clinical trials in the ICU setting and may enable a more nuanced appraisal of the impact of levosimendan in those situations.

DECLARATIONS

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