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REVIEW

Levosimendan to facilitate weaning from cardiorespiratory support in critically ill patients: current evidence and future directions

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ABSTRACT

Appropriate weaning is of crucial importance for critically ill patients requiring respiratory support. However, a remarkable proportion of them are difficult to wean. Levosimendan is a positive inotropic agent characterized by vasodilatory properties, which is used for the treatment of acute decompensated heart failure or in patients needing inotropic treatment, including cardiogenic shock, septic shock, pulmonary hypertension and right ventricular dysfunction, needed for hemodynamic support in patients with diuretic resistance, and weaning either from ventilator or from extracorporeal membrane oxygenation. This position paper will discuss the use of levosimendan in facilitating weaning from cardiorespiratory support in critically ill patients, according to available evidence and the personal experience of a group of Italian Experts.

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KEY WORDS: Ventilator weaning; Simendan; Respiration, artificial; Extracorporeal membrane oxygenation.

Traditional inotropes, vasopressors and the intra-aortic balloon pump (IABP) have a major role in the stabilization of patients with heart failure in the intensive care setting. However, these therapies are not without their drawbacks. Indeed, inotropes are associated with increased mortality and major morbidity, due to higher oxygen consumption and the risk of ischemia and arrhythmias,[1, 2] while current evidence does not support the indiscriminate use of IABP in this population.[3, 4] Therefore, venoarterial extracorporeal membrane oxygenation (VA-ECMO) is becoming increasingly used for the short-term management of patients in whom pharmacological support is not able to adequately restore cardiac output.[5] However, despite it allows organ support, ECMO is not a cure, and up to 35% of patients with cardiogenic shock may not restore an adequate heart function and hence will possibly fail weaning.[6]

Mechanical ventilation is a well-established supportive treatment for patients who experience various forms of respiratory failure. However, although it has clear benefits, mechanical ventilation is not without risks: indeed, prolonged mechanical ventilation can lead to increased risk of pneumonia, barotrauma, tracheal injuries and musculoskeletal deconditioning. On the other hand, delayed weaning is associated with increased morbidity and mortality, as well as a longer length of hospital stay.[7, 8]

Appropriate weaning is therefore of crucial importance for patients on mechanical ventilation. However, a remarkable proportion of them — up to 30% — are difficult to wean.[7, 9-11] One reason of difficulties in weaning is the development of diaphragm weakness in intubated patients, due to mechanical ventilation.[12-14] In addition, weaning from mechanical ventilation may greatly increase left ventricular filling pressure and pulmonary artery pressure, especially in those subjects with cardiac and/or pulmonary comorbidities.[11]

Levosimendan is a positive inotropic agent characterized by vasodilatory properties, which is used for the treatment of acute decompensated heart failure or in patients needing inotropic treatment, including cardiogenic shock, septic shock, pulmonary hypertension and right ventricular dysfunction, needed for hemodynamic support in patients with diuretic resistance, and weaning either from ventilator or from extracorporeal membrane oxygenation.[11] A detailed review of the use of levosimendan in those settings goes beyond the scopes of the present article; this position paper will rather discuss the use of levosimendan in facilitating weaning from cardiorespiratory support in critically ill patients, according to available evidence and the personal experience of a group of Italian Experts.

Levosimendan: an overview of the mechanism of action and the pharmacological rationale in weaning

Levosimendan exerts its action by multiple mechanisms (Table I) (unpublished authors' data). Among them, the most relevant is the sensitization of troponin C to calcium in cardiac muscle: this leads to a unique feature of levosimendan, *i.e.*, a positive inotropic effect without a noticeable increased consumption of oxygen in the myocardium.[11, 15] Since troponin in respiratory muscles resembles cardiac troponin, levosimendan may enhance muscular contractility as well,[16-19] although these findings were recently challenged.[20] Furthermore, levosimendan opens ATP-sensitive potassium (KATP) channels present in the vascular smooth muscle cells, thus promoting vasodilation.[11, 21] Sensitization of troponin C and the opening of KATP channels contribute to the inotropic and cardioprotective effects of levosimendan. At higher doses, the drug also inhibits the phosphodiesterase type 3 (PDE3) inhibitor.[11, 21] Remarkably, the effects of levosimendan are not influenced by the concomitant use of beta-blockers.[22]

Levosimendan in weaning from VA-ECMO

A first pilot report on levosimendan in patients weaning from VA-ECMO was published in 2013.[23] In total, six consecutive patients with cardiogenic shock received femorofemoral VA-ECMO support and levosimendan 24 hours before the planned weaning. A group of 11 patients treated with traditional inotropes served as historical control. The weaning rate was 83.33% with levosimendan *versus* 27.3% with traditional inotropes; the survival rate was 66.66% and

TABLE I.—*Mechanisms of action of levosimendan (unpublished authors' data).*

Action	Mechanism
Positive inotropism	Calcium sensitization by saturating troponin C myofilaments of the cardiomyocytes
Vasodilation	Hyperpolarization by ATP-sensitive K+ channels existent on the sarcolemma of vascular smooth muscle cells
Cardioprotection	Protection of mitochondria in ischemia-reperfusion mechanism in the cardiomyocytes
Phosphodiesterase inhibition	cAMP elevation caused by alterations in intracellular Ca2+ concentration
Neurohormone, cytokine and biomarker properties	Not entirely understood, several cellular processes involved (from preservation of endothelial function to the inhibition of platelet aggregation)

36.4%, respectively. Only, three of six patients on levosimendan required inotropic/vasopressor support after ECMO interruption, compared with 11/11 in the historical comparison group.

More recently, Distelmarier *et al.* evaluated the impact of levosimendan on survival and failure of VA-ECMO weaning in 240 patients undergoing cardiovascular surgery, 75% of whom received levosimendan.[24] At a median follow-up of 37 months (interquartile range [IQR]: 19–67 months), 65% of patients had died. Statistical analysis discussed an association between levosimendan treatment and successful ECMO weaning (adjusted hazard ratio [HR]: 0.41; 95% CI: 0.22-0.80; P=0.008], short-term (30 days) mortality (adjusted HR: 0.52; 95% CI: 0.30–0.89; P=0.016) and long-term mortality (adjusted HR: 0.64; 95% CI: 0.42–0.98; P=0.04). These data, obtained in a larger sample of patients, suggest there is an association between levosimendan therapy and improved survival in patients undergoing ECMO support after cardiovascular surgery.

In a prospective trial, conducted at the intensive care unit (ICU) of a large tertiary care center, Sangalli *et al.* investigated the endothelial and hemodynamic effects of levosimendan in ten patients with cardiogenic shock supported with VA-ECMO.[25] Flow-mediated dilatation increased after levosimendan therapy (from 3.2±4.2% to 17.8±10.4%; P<0.001). Cardiac index increased from 1.93±0.83 to 2.64±0.97 L/min/m^2 (P=0.008) and mixed venous oxygen saturation increased as well (from 66.0% to 71.5%; P=0.006). Arterial lactate levels decreased over time (from 1.25 to 1.05 mmol/L; P=0.004). This improved hemodynamics made it possible to reduce ECMO oxygenation blood flow from 1.92±0.65 to 1.12±0.49 L/min/m^2 (P<0.001).

In a very recent study, weaning from extracorporeal life support with levosimendan help was evaluated in a retrospective before-and-after study.[26] A total of 64 patients were evaluated; of them, 26 (41%) received levosimendan, while the other ones received milrinone. Successful weaning was achieved in 24 (92%) patients on levosimendan *versus* 30 (79%) on milrinone. Moreover, fewer patients on levosimendan required an intra-aortic balloon pump for weaning (2 [7.7%] *versus* 15 [40%]; P=0.008). Mortality rates were similar in the two groups (28-day mortality: 35% *vs.* 40%; 180-day mortality: 50% *vs.* 44%).

Last, Vally *et al.* evaluated the impact of levosimendan on VA-ECMO weaning in patients in ICU.[27] In total, 38 propensity-matched patients on levosimendan and 65 not receiving this molecule were evaluated. In those patients on levosimendan, left ventricular ejection fraction (LVEF) increased (from 21.5±9.1% to 30.7±13.5%; P<0.0001) as well as aortic velocity-time integral (from 8.9±4.0 cm to 12.5±3.8 cm; P=0.002) 24 hours after drug infusion. On statistical analysis, levosimendan was the only factor associated with a significant reduction in VA-ECMO weaning failure rates (HR: 0.16; 95% CI: 0.04–0.70; P=0.01). Survival at 30 days was 78.4% with levosimendan and 49.5% without levosimendan (P=0.02), but this difference lost significance after propensity matching.

Levosimendan in weaning from mechanical ventilation: clinical evidence

Levosimendan has been clinically evaluated in two main studies on difficult-to-wean patients on mechanical ventilation, given its potential effect also in the respiratory muscles and, in particular, on the diaphragm (Table II).[9, 28]

In the first study, with a prospective, observational design, Sterba *et al.* evaluated the role of levosimendan in improving cardiac performance and the success rate of weaning from mechanical ventilation in 47 difficult-to-wean (ventilatory dependence ≥10 days and failed weaning or extubation due to respiratory insufficiency) patients with impaired cardiac function hospitalized in the ICU.[9] In total, 12 patients with impaired left ventricular performance (LVEF <40%) and on diuretic and vasodilator treatment received a 24-hour infusion of levosimendan. This therapeutic strategy was associated with increased LVEF (28.3% before *vs.* 34.6% after; P=0.04) and PaO_2/FIO_2 ratio (179 *vs.* 197 mmHg; P=0.002), and reduced FIO_2 (0.45 *vs.* 0.39; P=0.01). Moreover, seven out of 12 patients on levosimendan were successfully weaned (P=0.02 *vs.* no levosimendan), and six were discharged. After 2 years,

TABLE II.—*Studies on levosimendan in weaning from mechanical ventilation.*[9, 28]

Study	Design	Patients	Main outcomes
Sterba *et al.*[9]	Prospective, observational study	12 patients in ICU ventilatory dependent for ≥10 days received levosimendan	Increased LVEF after levosimendan (28.3% before *vs.* 34.6% after; P=0.04) Improved PaO2/FIO2 ratio (179 mmHg *vs.* 197mmHg; P=0.002) Reduced FIO2 (0.45 v 0.39, P=0.01). 7 out of 12 patients (58%) were successfully weaned, and 6 (50%) survived to discharge
Ouanes-Besbes *et al.*[28]	Prospective, observational pilot study	10 patients with COPD with weaning difficulties received dobutamine followed by levosimendan	Levosimendan had a greater effect on pulmonary artery occlusion pressure at the shift from mechanical to spontaneous breathing than dobutamine (median PAOP increase: 9 *vs.* 5 mmHg; P<0.01)

Ouanes-Besbes *et al.* prospectively compared the short-term hemodynamic effects of levosimendan with those of dobutamine in ten patients with chronic obstructive pulmonary disease who had difficulties in weaning due to increased left ventricular filling pressure (increase >10 mmHg of pulmonary artery occlusion pressure [PAOP] at the shift from mechanical to spontaneous breathing [SB]).[28] Patients received 1-hour infusion of 7 μg/kg/min of dobutamine, followed by 24-hour infusion of 0.2 μg/kg/min of levosimendan. Both drugs reduced significantly the level of PAOP increase at SB, but the change was greater with levosimendan (median PAOP increase [IQR]: 5 [2] *vs.* 9 [4] mmHg, respectively; P<0.01).

Moreover, in a recent pilot study, Kaltsi *et al.* investigated the efficacy of levosimendan in 11 difficult-to-wean patients with an impaired performance of the left ventricle.[29] After levosimendan administration, LVEF increased by 6% (from 30±10 to 3±3%; P=0.01). End-spontaneous breathing trial peak velocity and other relevant parameters also increased. Nine out of the 11 patients were successfully weaned. The Authors concluded that in patients with left ventricular dysfunction who are difficult to wean from mechanical ventilation, levosimendan contributes to successful weaning by improving both systolic and diastolic left ventricular function.

Expert opinion

In recent years, the use of levosimendan has broadened to different settings, among which the pre- and post-operative use in patients undergoing cardiac surgery and in facilitating weaning from ECMO or mechanical ventilation.

In particular, some characteristics of levosimendan make this drug particularly suitable for weaning from VA-ECMO, namely the inotropic effect without an increase in myocardial oxygen consumption, the lack of a proarrythmic effect or interaction with beta-blockers, the systemic, pulmonary and coronary vasodilation (anti-ischemic effect), the cardioprotective effect against the ischemia/reperfusion injury due to the inhibition of the mitochondrial apoptotic pathway, the anti-inflammatory activity, and its beneficial action on renal and hepatic flow.[21] Moreover, its long-lasting action (up to 8-9 days) due to circulating active metabolites, could be particularly useful since it could allow a gradual weaning and provide a continuous support in the critical immediate post-ECMO period. Remarkably, available clinical data in this setting seem promising, showing a reduction in the need for high-dose inotropes, an increased weaning rate and an improved endothelial function. Increased short- and long-term survival rates have also been reported in patients who had undergone VA-ECMO implantation after cardiac surgery or weaning from mechanical ventilation, along with those with ventilation dependence. Larger studies, however, possibly with a prospective design, are needed to draw definitive conclusions about the use of levosimendan in the weaning process from ECMO or mechanical ventilation.

Based on pathophysiological and pharmacological rationale, we propose two algorithms that include the use of levosimendan in patients difficult to wean from ECMO and ventilator, or ventilated for more than 7 days, with myocardial dysfunction (Figure 1). These algorithms represent the current clinical practice in the Authors'

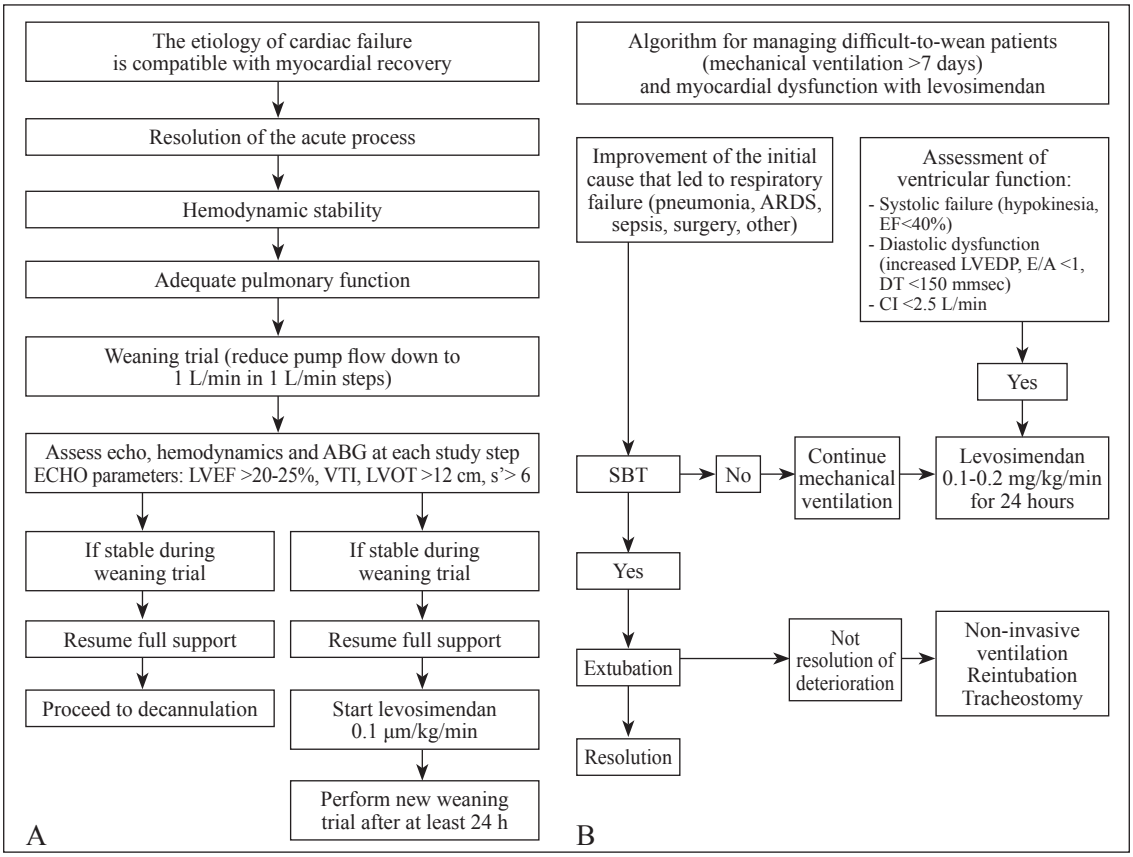

Figure 1.—Algorithms for weaning from (A) ECMO and (B) mechanical ventilation, which include levosimendan.

Institutions and are based on pathophysiology, local experience and the small amount of published literature on these subpopulations of critically ill patients. In most cases ECMO is started as a bridge to heart recovery, hence the presence of a reversible pathology is the first requisite to start a weaning process. Secondly, the risks of prolonging ECMO support must be weighed against the degree of recovery, and weaning can be attempted once a sufficient cardiac function has been restored.[30] Despite matching these criteria however, patients may fail the initial weaning trial. In this case, the addition of levosimendan appears in preliminary studies to confer a benefit on weaning and even on survival.

Despite the established or postulated benefits of levosimendan to facilitate weaning from cardiorespiratory support, it might be argued that weaning does not mean survival. In fact, up to 65% of patients successfully weaned off VA-ECMO do not survive to hospital discharge.[31, 32] Besides this, recently published RCTs on the use of levosimendan in different settings (LEVO-CTS, CHEETAH, LEOPARDS) did not show an increased survival in the groups receiving levosimendan.[33-35] However, we believe that the main strength of such studies is the additional evidence to the safety profile of the drug, while the likely effect of a single intervention on mortality in such complex critically ill patient is very difficult to determine. This might be even more true in very selected and severely diseased populations, such as those examined in the present work, where weaning represents a determinant limiting step in the process of care.

In order to evaluate the real-world use of levosimendan in these settings, the Authors of the present paper are starting an Italian Registry that will collect data from all the Centers using the drug to facilitate weaning from cardiorespiratory

support. The information gathered from this registry will possibly help in designing a prospective trial to further clarify the potential of levosimendan in this setting.

Conclusions

Levosimendan is particularly suitable for a gradual weaning from VA-ECMO and promising studies on its role in providing a continuous support in the post-ECMO period are available.

Prospective trials will further contribute to better define the use of Levosimendan in the weaning process from ECMO or mechanical ventilation.

Key points

• Levosimendan is a positive inotropic agent characterized by vasodilatory properties, which is used for the treatment of acute decompensated heart failure or in patients needing inotropic treatment.

• Levosimendan has a potential effect in facilitating weaning from cardiorespiratory support in critically ill patients and here available evidence and the personal experience of Italian Experts are reported.

• Two algorithms that include the use of levosimendan in patients difficult to wean from ECMO and ventilator, or ventilated for more than 7 days, with myocardial dysfunction are also proposed.

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