



### Original Article

## Levosimendan as a rescue therapy for low output syndrome after cardiac surgery

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### Abstract

**Background:** The calcium sensitizer levosimendan has been shown to improve outcomes in patients with low cardiac output syndrome (LCOS) following cardiac surgery. We assessed its efficacy when used as a rescue therapy in the postoperative setting rather than as a prophylactic preoperative treatment.

**Methods:** According to our institutional protocol, 18 patients with LCOS that persisted despite conventional inotropic therapy received a 24-hour infusion of levosimendan at 0.1 µg/kg/min. Hemodynamic parameters and clinical outcomes were monitored and statistically analyzed.

**Results:** Ejection fraction (EF) increased significantly from  $29 \pm 5\%$  to  $41.6 \pm 2.7\%$  within 48 hours of initiating levosimendan. This improvement was accompanied by a significant increase in cardiac output from  $3.7 \pm 0.5$  L/min to  $5.6 \pm 0.8$  L/min after 48 hours, along with significant dose reductions in concomitant vasopressors and inotropes. Inotropic support was significantly reduced at the 12-hour assessment compared to the immediate postoperative period and continued to decline over the 48-hour observation window. The norepinephrine dose showed a significant reduction at 48 hours. The overall perioperative mortality was 11%.

**Conclusion:** Our study suggests that levosimendan is an effective rescue therapy for managing LCOS postoperatively. Its administration should be part of a controlled regimen that avoids unnecessary delays and allows for the concurrent use and monitoring of conventional inotropes.

### KEYWORDS

Levosimendan; Low cardiac output syndrome; Cardiac surgery; Rescue therapy; Inotrope

### Article History

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### Introduction

The incidence of low cardiac output syndrome (LCOS) following cardiac surgery ranges between 10% and 20% [1], with an associated mortality rate as high as 16.9%, a stark contrast to the 0.9% rate observed in patients without LCOS [2]. Beyond higher mortality, this syndrome increases the risk of postoperative cardiac dysfunction, kidney failure, and prolonged intensive care unit (ICU) and hospital stays [3]. Susceptibility to LCOS is

influenced by various factors, including pre-existing reductions in left and/or right ventricular function or a recent myocardial infarction [4]. The surgical procedure itself also modulates risk, with combined coronary artery bypass grafting (CABG) and valve surgery conferring a higher risk than isolated CABG [5].

First-line management of LCOS involves inotropic agents, while mechanical support

devices are reserved for cases refractory to pharmacologic therapy. However, conventional inotropes—primarily catecholamines and phosphodiesterase inhibitors are associated with increased complications and mortality rates after cardiac surgery [6].

Levosimendan is a calcium-sensitizing inotrope and vasodilator with over two decades of clinical use. Its mechanism of action involves calcium-dependent binding to cardiac troponin C, which enhances myocardial contractility without increasing oxygen demand. Concurrent vasodilation is achieved through the opening of ATP-sensitive potassium (KATP) channels in vascular smooth muscle [7]. By activating mitochondrial KATP channels in cardiomyocytes, levosimendan also provides short-term (preconditioning, anti-stunning) and long-term (anti-remodeling, anti-inflammatory) cardio-protection [7]. Levosimendan itself has an elimination half-life of approximately 1 hour; however, it produces an active circulating metabolite that reaches its peak concentration 5 to 6 days after the infusion is stopped [7]. In addition to its original indication for acutely decompensated heart failure, it has also been used to stabilize patients undergoing cardiac surgery. Abundant literature from exploratory studies supports the rationale for its use in this indication, which is also supported by its benign effect on kidney function [8].

A widely accepted consensus recommends initiating levosimendan the day before surgery at a dose of 0.1  $\mu$ g/kg/min infused over 24 hours. However, numerous studies have proven the efficacy of its perioperative use in both on-pump and off-pump procedures [9–11]. In this study, we present our experience with the use of levosimendan as a rescue therapy for LCOS in patients undergoing cardiac surgery.

## Patients and Methods

### Study Design and patient population

We conducted a retrospective analysis of 18 patients who received levosimendan as rescue therapy for persistent LCOS in the perioperative period at our institution from April 2021 to April 2023.

### Exclusion criteria

1. Patients diagnosed with LCOS with continued perioperative myocardial ischemia
2. Patients that had and IABP inserted during which Levosimendan was administered.
3. Patients that did not receive the full dose of Levosimendan infusion.
4. Successfully resuscitated Post arrest Patients before Levosimendan infusion.

### Inotropic Support Protocol

According to our institutional protocol, inotropic support is initiated after weaning from cardiopulmonary bypass. The standard regimen includes:

- Epinephrine: Administered up from 1 ml/hr to 30 ml/hr
- Norepinephrine: Used as needed for vasopressor support.
- Milrinone: Added if signs of right ventricular dysfunction are present.

### Levosimendan Administration

Levosimendan infusion was initiated if signs of LCOS persisted in the immediate and early postoperative period after the initiation of standard inotropic support. This few hours window allows for the full effect of adrenergic inotropes, haemodynamic and fluid resuscitation to be established. The general criteria for initiating levosimendan were usually:

- Mean Arterial Pressure (MAP) < 60 mmHg
- Signs of organ dysfunction (e.g., elevated lactate or oliguria)
- Low cardiac output less than 4 l/min

Levosimendan was administered without a loading dose at a rate of 0.1  $\mu$ g/kg/min and continued for 24 hours.

### Hemodynamic Monitoring and Data Collection

Hemodynamic monitoring was performed using invasive arterial pressure monitoring, a central venous line, and echocardiography (Philips iE33 ultrasound machine). Key hemodynamic parameters were calculated, including stroke volume (SV), and VTI in order to calculate the cardiac output (COP).

### Echocardiographic Assessment

Echocardiographic assessments were performed at the following time points:

- Intraoperatively: Transesophageal echocardiography (TEE) was performed in the operating room after separation from bypass.
- Postoperatively: Transthoracic echocardiography (TTE) was performed in the ICU before starting levosimendan and followed up for the subsequent 48-hour period.

### Statistical analysis

Continuous variables are expressed as mean and standard deviation (SD), while categorical variables are expressed as numbers and percentages. A paired t-test and a Friedman test were used to compare repeated measures. A p-value of  $< 0.05$  was considered statistically significant. All statistical analyses were performed using SPSS software (SPSS Inc., Chicago, IL, USA).

*Table 1: Preoperative characteristics of the patients who received levosimendan*

Parameter	N= 18
<b>Surgical Procedure, n (%)</b>	
CABG	9 (50%)
CABG + MVS	4 (22.2%)
Double Valve	3 (16.7%)
Mitral Valve	2 (11.1%)
<b>Diabetic, n (%)</b>	5 (27.8%)
<b>Creatinine (mg/dL), Mean <math>\pm</math> SD</b>	1.5 $\pm$ 0.3
<b>NYHA Class IV, n (%)</b>	2 (11.1%)
<b>Preoperative EF (%), Mean <math>\pm</math> SD</b>	47.9 $\pm$ 6.3
<b>Age (years), Mean <math>\pm</math> SD</b>	60.4 $\pm$ 6.3
<b>Sex, n (%)</b>	
Male	14 (77.8%)
<b>EuroSCORE II, Mean <math>\pm</math> SD</b>	3.5 $\pm$ 0.5

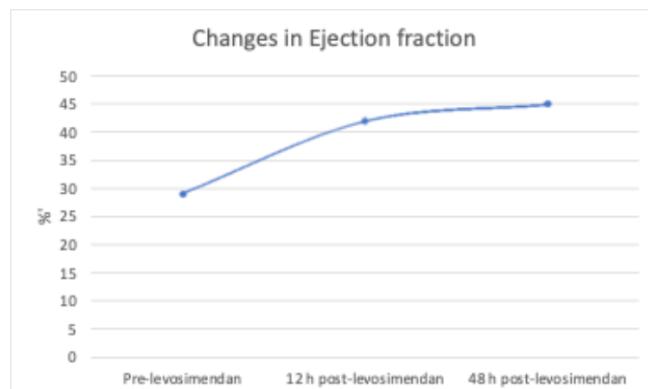
CABG, coronary artery bypass grafting; MVS, mitral valve surgery replacement/repair; DVR, double valve replacement; MVR, mitral valve replacement; NYHA, New York Heart Association; EF, ejection fraction

(n=4, 22.2%), double valve surgery (n=3, 16.7%), and mitral valve surgery (n=2, 11.1%) (Table 1).

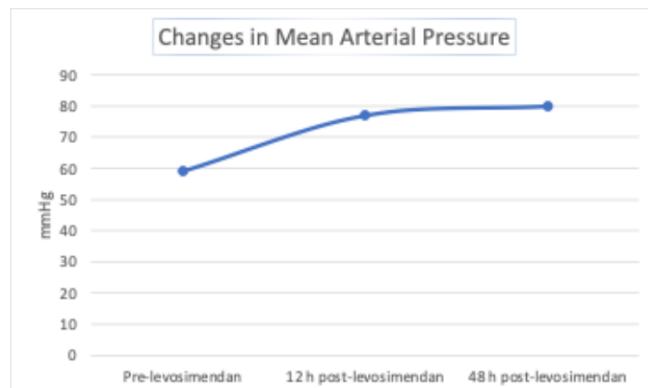
### Hemodynamic and Clinical Outcomes

All patients received a continuous 24-hour levosimendan infusion according to the protocol.

- **Cardiac Function:** A statistically significant improvement in ejection fraction (EF) was observed. The mean EF increased from an immediate postoperative value of  $29 \pm 5\%$  to  $41.6 \pm 2.7\%$  at 48 hours.
- **Hemodynamic Parameters:** Mean arterial pressure (MAP) and cardiac output showed statistically significant improvements at follow up assessment compared to immediate postoperative measurements.
- **Right Ventricular Function:** Right ventricular (RV) function, assessed by tricuspid annular plane systolic excursion (TAPSE), and pulmonary artery pressure showed trends toward improvement; however, these findings were not statistically significant in this study. (Table 2; Figure 1 and Figure 2)



*Figure 1: Ejection fraction change at 12 and 48 hours postoperative*



*Figure 2: Changes in MAP at 12 and 48 hours*

## Results

### Patient Characteristics

A total of 18 patients were enrolled. The mean age was  $60.4 \pm 6.3$  years, and 14 (77.7%) were male. The mean EuroSCORE II for this cohort was  $3.5 \pm 0.5$ . The surgical procedures performed were coronary artery bypass grafting (CABG) (n=9; 50%), combined CABG and mitral valve surgery

Table 2: Hemodynamic parameters at 12 and 48 hours postoperative. Data are presented as mean and SD

Parameter	Pre Levosimendan	Post-Levosimendan (12h)	Post-Levosimendan (within -48h)	p-value (Pre vs. 12h)	p-value (Pre vs. 48h)
<b>Ejection Fraction (%)</b>	29.2 ± 3.4	35.0 ± 5.7	41.6 ± 2.7	< 0.001	< 0.001
<b>Mean Arterial Pressure (mmHg)</b>	59.1 ± 3.0	65.3 ± 3.8	77.3 ± 3.8	< 0.001	< 0.001
<b>Cardiac Output (L/min)</b>	3.7 ± 0.5	-	5.6 ± 0.8	< 0.001	< 0.001
<b>TAPSE (mm)</b>	16.1 ± 1.2	-	16.9 ± 1.5	-	0.016

TAPSE, Tricuspid Annular Plane Systolic Excursion

### Inotropic Support and Interventions

- Inotrope Doses:** Inotropic support was significantly reduced at the 12-hour assessment compared to the immediate postoperative period and continued to decline over the 48-hour observation window. The dose of norepinephrine showed a slight, non-significant change at 12 hours but then demonstrated a significant drop at 48 hours (Table 3; Figure 3)
- Mortality:** The overall perioperative mortality in the rescue group was 11% (n=2). Both deceased patients had undergone CABG; one developed acute renal impairment requiring continuous veno-venous hemodiafiltration (CVVHDF), and the other experienced intractable ventricular arrhythmias. (Table 4)

Two patients received Levosimendan late after 24 hours. ; One case had severe vascular Vasoplegia that resolved later in the postoperative course delaying the ability to infuse Levosimendan, the other patient was diagnosed with perioperative myocardial infarct and was admitted to the operation room for revascularization , then later in the postoperative settings received the infusion of Levosimendan ,

they demonstrated a substantial reduction in both norepinephrine and epinephrine doses over the 24 hours following drug initiation, with decreases ranging from 40% to 57%. (Table 5)

### Discussion

This retrospective study of 18 patients demonstrated that levosimendan showed effectiveness as a rescue therapy for persistent LCOS following cardiac surgery when initiated postoperatively after a window of conventional inotropic and volume optimization. The protocol resulted in statistically significant improvements in key hemodynamic parameters. Ejection fraction increased significantly, accompanied by improvements in mean arterial pressure and cardiac output. Importantly, levosimendan therapy enabled a significant reduction in the doses of conventional inotropes and vasopressors, suggesting improved intrinsic cardiac contractility and reduced dependence on catecholamine support. The overall perioperative mortality was 11%. These findings support the use of a delayed "rescue" approach to levosimendan therapy as an effective alternative to prophylactic administration for managing postoperative LCOS.

Table 3: Withdrawal of Inotropic and Vasopressor Support After Levosimendan. Data are presented as mean and standard deviation

Agent	Pre-Levosimendan	12h Post-Levosimendan	24h Post-Levosimendan	48h Post-Levosimendan	p-value
<b>All Patients Epinephrine (ml/hr)</b>	8.61 ± 2.65	5.83 ± 3.22	3.72 ± 2.87	2.83 ± 2.82	< 0.001
<b>All patients Norepinephrine (ml/hr)</b>	8.39 ± 2.66	8.94 ± 2.37	8.28 ± 1.95	3.56 ± 1.50	< 0.001
<b>Milrinone (ml/hr)</b>	0.21 ± 0.24	0.00 ± 0.00	-	-	0.002

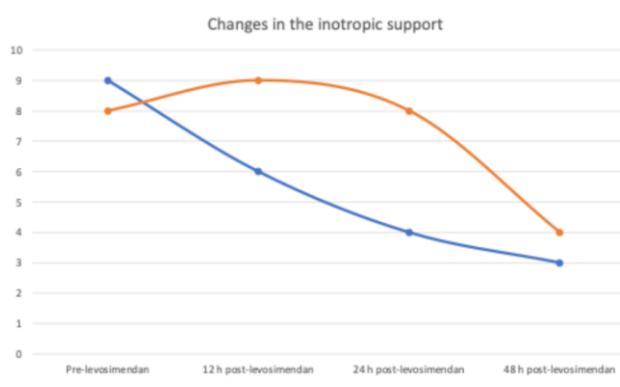


Figure 3: Changes in inotropes at 12, 24 and 48 hours

Levosimendan has been extensively researched for over two decades. A major meta-analysis including over 28,000 patients from 177 randomized trials identified levosimendan as the only inotropic agent associated with a significant improvement in survival during cardiac surgery [12]. However, the landscape is nuanced. Three large, multicenter, randomized, placebo-controlled trials—LICORN [13], CHEETAH [14], and LEVO-CTS [15]—concluded that while levosimendan is safe and effective for hemodynamic support, it did not significantly reduce 30-day mortality compared to placebo, except in a specific subgroup of patients with low ejection fraction undergoing isolated CABG. These trials also found no significant differences in the duration of mechanical ventilation, need for renal replacement therapy, incidence of hypotension, cardiac arrhythmias, or ICU stay [16]. In 2015, a European expert panel recommended the prophylactic use of levosimendan in patients with compromised myocardial function, advising that the infusion be started the day before surgery at a

dose of 0.1  $\mu\text{g}/\text{kg}/\text{min}$  for 24 hours without a bolus [17].

Our study deviates from the well-established preoperative use and instead focuses on the efficacy of levosimendan as a rescue therapy in the immediate postoperative period. The decision to undertake this study was driven by our early clinical observations, where the first patients receiving rescue levosimendan therapy demonstrated rapid and significant clinical improvement, suggesting a potent therapeutic effect worthy of formal analysis. We initiated the infusion if LCOS persisted for a few hours despite optimized conventional inotropic support, allowing a sufficient window for conventional inotropes to take effect while ensuring levosimendan was started before the onset of significant end-organ damage. This approach is comparable to the study by Beiras-Fernandez et al. [18], who used a threshold of six hours, and differs from the regimen described by Toller et al. [17], where the infusion was started after the release of the aortic cross-clamp.

Our findings demonstrate a significant improvement in both cardiac output and ejection fraction following the initiation of rescue levosimendan. This was accompanied by a significant reduction in the required doses of conventional inotropes, reflecting an improvement in intrinsic cardiac contractility. Vasopressor doses remained almost unchanged within the first 12 hours but showed a significant drop after 48 hours.

Table 4: Hemodynamic and Inotropic Profile of Non-Surviving Patients

Parameter	Pre-Levosimendan	12h Post-Levosimendan	24h Post-Levosimendan	48h Post-Levosimendan
<b>Patient 7R</b>				
Cardiac Output (L/min)	2.5	-	-	3.5
Epinephrine (ml/hr)	12	12	10	10
Norepinephrine (ml/hr)	7	8	10	9
Milrinone (ml/hr)	0	0	-	-
<b>Patient 17R</b>				
Cardiac Output (L/min)	4.0	-	-	5.2
Epinephrine (ml/hr)	14	16	14	13
Norepinephrine (ml/hr)	12	12	10	8
Milrinone (ml/hr)	0.75	0	-	-

Table 5: Effect of delayed levosimendan infusion on inotropic and vasopressor supports

	Pre-Levosimendan	12h post-Levosimendan	24h post-Levosimendan	48h post-Levosimendan	p-value (Pre vs 24h)
<b>Patients that had Late Start of Levosimendan (Adrenaline dose)</b>	7.00 ± 0.00	5.50 ± 0.71	4.00 ± 1.41	3.00 ± 0.00	
<b>Patients that had Late Start of Levosimendan (Noreadrenaline dose)</b>	8.50 ± 2.12	8.50 ± 0.71	9.00 ± 1.41	5.00 ± 1.41	
<b>All Patients Epinephrine (ml/hr)</b>	8.61 ± 2.65	5.83 ± 3.22	3.72 ± 2.87	2.83 ± 2.82	< 0.001
<b>All patients Norepinephrine (ml/hr)</b>	8.39 ± 2.66	8.94 ± 2.37	8.28 ± 1.95	3.56 ± 1.50	< 0.001

These results align with the findings of several other groups that investigated the perioperative use of levosimendan in patients undergoing CABG [19–21]. In contrast, one study by Lahtinen et al. [22] reported an increased need for vasopressors, which was likely attributable to their use of a bolus administration leading to a drop in systemic vascular resistance—a practice we avoided in our protocol. The sustained hemodynamic improvement observed 48 hours after the infusion is consistent with the pharmacokinetic profile of levosimendan's active metabolite, which has a long elimination half-life of approximately 80 hours [7].

The overall mortality in our patients was 11%. Both non-survivors were CABG patients; one required renal replacement therapy and the other succumbed to ventricular arrhythmias. This outcome was associated with an increased need for catecholamine support post-infusion, suggesting that a poor myocardial response to levosimendan is a negative prognostic indicator in escalating cardiogenic shock, particularly high mortality.

While two patients received Levosimendan late after 24 hours. The analysis of the two patients who received Levosimendan significantly later than the institutional standard reveals a clinically important but complex picture. The reasons for delayed infusion were; One case had severe vascular Vasoplegia that resolved later in the postoperative course delaying the ability to infuse Levosimendan, the other patient was

diagnosed with perioperative myocardial infarct and was admitted to the operation room for revascularization, then later in the postoperative settings received the infusion of Levosimendan after resolving the myocardial ischaemia. Both patients survived and recovered from surgery. For both individuals, the delayed infusion was associated with a clear and positive weaning trend in vasopressor requirements. Specifically, each patient demonstrated a substantial reduction in both norepinephrine and epinephrine doses over the 24 hours following drug initiation, with decreases ranging from 40% to 57%. This indicates that Levosimendan retained its pharmacological activity and provided hemodynamic benefit even when administered at 24 and 48 hours post-operatively.

However, this positive effect must be interpreted within a broader context. Despite the successful weaning trend, the absolute vasopressor doses for these two patients at the 48-hour post-operative mark remained notably higher than the group average. Their requirements for norepinephrine, in particular, were elevated compared to their peers who received early intervention. This may suggest that while the delayed infusion was beneficial, it may have been insufficient to fully reverse the established shock state, potentially resulting in an incomplete hemodynamic recovery compared to the early treatment group.

Crucially, it is impossible to determine the statistical significance of these observations. With

only two cases in the delayed cohort, any quantitative comparison is rendered faulty and unreliable; the limited sample size means the observed differences could plausibly be due to chance rather than a true effect of timing. Therefore, while the data suggests a compelling clinical narrative that delayed administration is linked to desired effects of Levosimendan, but might be with persistently higher vasopressor needs, this finding must be considered hypothesis-generating rather than conclusive. It underscores the critical need for early intervention and highlights the necessity of a larger, dedicated study to statistically validate the impact of timing on Levosimendan's efficacy in weaning vasopressor support.

The pattern of inotrope and vasopressor withdrawal following levosimendan initiation revealed a critical prognostic distinction between survivors and non-survivors. In the overall cohort, a clear and favourable pattern emerged: a rapid and significant reduction in epinephrine requirements indicated a positive inotropic response, while a delayed but substantial drop in norepinephrine doses suggested improved perfusion that eventually overcame initial vasodilation [7, 19]. Conversely, the two patients who died exhibited a divergent, ominous pattern. Their continued high demand for catecholamine support after receiving levosimendan implied a failure to respond to its inotropic and vasodilatory effects. This lack of response, leading to escalating cardiogenic shock, was a strong negative prognostic indicator, directly associated with their fatal outcomes, a finding consistent with the work of Beiras-Fernandez et al. [18]. Thus, the trajectory of vasopressor and inotrope requirements post-levosimendan served as a real-time marker of therapeutic efficacy and ultimate survival.

### Limitations

This study has several limitations. We acknowledge that LCOS is not a common scenario postoperatively, yet a larger number of patients is still required in order to draw definitive conclusions. Additionally, the heterogeneity of patient diagnoses, while reflecting real-world clinical scenarios in the cardiac ICU, is a limiting factor for statistical analysis. There was not

definite timing of administration of levosimendan. In most cases it was initiated within the first 12hrs postoperatively, yet it ranged from a few hours up to 48 hrs postoperatively in this cohort. The correlation between the improvement in cardiac parameters and the administration of levosimendan as a single factor is difficult to establish definitively without a larger, controlled study.

The retrospective design also imposed limitations on hemodynamic data completeness. Although cardiac index and systemic vascular resistance are valuable metrics for this study, the data required for systemic vascular resistance calculation were not documented for all of the 18 patients, restricting a more comprehensive analysis."

### Conclusion

Our study suggests that levosimendan is an effective additional therapy for managing LCOS in the postoperative setting, and according to patients' response may have a prognostic value, that may lead to an earlier step wise approach in treating LCOS. However, its administration should be part of a well-controlled regimen that avoids unnecessary delays and allows for the concurrent use and monitoring of conventional inotropes.

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