*Modern American Journal of Medical and Health Sciences*
**ISSN (E):** 3067-803X
Volume 01, Issue 09, December, 2025
**Website:** usajournals.org


# IMPACT OF DIFFERENT CARDIOTONIC AGENTS ON MYOCARDIAL FUNCTION AFTER CORONARY ARTERY BYPASS GRAFTING

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**Abstract**

**Background**: Postoperative myocardial dysfunction and low cardiac output syndrome (LCOS) remain among the most serious complications following coronary artery bypass grafting (CABG), significantly increasing morbidity, length of intensive care unit (ICU) stay, and early mortality. Optimal cardiotonic support is therefore crucial in the early postoperative period. **Objective**: To compare the effects of different cardiotonic agents on myocardial function, hemodynamics, and early clinical outcomes in patients after CABG. **Methods**: A prospective comparative study was conducted from 2022 to 2025 at the Republican Specialized Scientific and Practical Medical Center of Cardiology, Fergana Regional Branch. A total of 180 patients who developed LCOS after CABG were enrolled and divided into three groups receiving dobutamine, milrinone, or levosimendan. Echocardiographic, hemodynamic, and metabolic parameters were assessed.

**Results**: Patients treated with levosimendan demonstrated significantly greater improvement in left ventricular ejection fraction (LVEF), cardiac index, and lactate clearance compared to dobutamine and milrinone ($p < 0.05$). ICU stay and incidence of postoperative heart failure were lower in the levosimendan group. **Conclusion**: Levosimendan provides superior myocardial support and improves early postoperative outcomes after CABG, suggesting its preferential use in patients with LCOS.

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## INTRODUCTION

Coronary artery bypass grafting (CABG) remains the gold standard surgical treatment for patients with advanced multivessel coronary artery disease, particularly in cases involving left main coronary artery stenosis, diffuse atherosclerotic involvement, or impaired left ventricular function. Over recent decades, significant advances have been achieved in surgical techniques, cardiopulmonary bypass technology, myocardial protection strategies, anesthetic management, and perioperative monitoring. These improvements have led to a reduction in perioperative mortality and major complications. However, despite these advancements, postoperative myocardial dysfunction remains a frequent and clinically significant complication following CABG[1-5].

Early postoperative myocardial dysfunction is reported to occur in approximately 20–30% of patients undergoing CABG and represents one of the leading causes of morbidity in the immediate postoperative period. This condition is multifactorial in origin and may result from intraoperative ischemia–reperfusion injury, myocardial stunning, systemic inflammatory response associated with cardiopulmonary bypass, incomplete revascularization, or pre-existing left ventricular dysfunction. The clinical manifestation of postoperative myocardial dysfunction often presents as low cardiac output syndrome (LCOS), a serious and potentially life-threatening condition[6-8].

Low cardiac output syndrome is characterized by an inability of the heart to maintain adequate systemic perfusion to meet metabolic demands, resulting in tissue hypoxia and organ dysfunction. Clinically, LCOS is associated with hypotension, reduced urine output, elevated serum lactate levels, metabolic acidosis, prolonged mechanical ventilation, increased need for renal replacement therapy, and extended intensive care unit (ICU) and hospital stays. Importantly, LCOS has been consistently linked to increased short- and long-term mortality following cardiac surgery, highlighting the critical importance of early recognition and effective management.

Pharmacological support with cardiotonic agents remains a cornerstone in the management of postoperative myocardial dysfunction and LCOS. These agents are commonly administered to enhance myocardial contractility, optimize cardiac

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output, and improve systemic perfusion during the vulnerable early postoperative period. However, cardiotonic drugs differ significantly in their pharmacodynamic properties, hemodynamic effects, and safety profiles, which may influence clinical outcomes[9].

Dobutamine, a synthetic β1-adrenergic agonist, is one of the most widely used inotropic agents in cardiac surgery. It increases myocardial contractility and heart rate through stimulation of β1-adrenergic receptors, leading to an increase in cardiac output. However, its use is associated with increased myocardial oxygen consumption, tachyarrhythmias, and a potential risk of ischemia, particularly in patients with compromised coronary perfusion or residual myocardial ischemia[10].

Milrinone, a phosphodiesterase-III inhibitor, exerts its inotropic and lusitropic effects by increasing intracellular cyclic adenosine monophosphate (cAMP) independently of β-adrenergic receptors. In addition to improving myocardial contractility, milrinone induces systemic and pulmonary vasodilation, thereby reducing both preload and afterload. These properties make milrinone particularly attractive in patients with pulmonary hypertension or right ventricular dysfunction. Nevertheless, its vasodilatory effects may lead to systemic hypotension, increased need for vasopressor support, and potential renal impairment.

Levosimendan represents a newer class of inotropic agents known as calcium sensitizers. It enhances myocardial contractility by increasing the sensitivity of cardiac troponin C to calcium without elevating intracellular calcium concentrations or myocardial oxygen consumption. Furthermore, levosimendan opens adenosine triphosphate-dependent potassium channels in vascular smooth muscle, resulting in vasodilation and improved coronary and microcirculatory blood flow. These unique mechanisms suggest potential cardioprotective and anti-ischemic effects, making levosimendan an attractive alternative in the management of postoperative myocardial dysfunction.

Despite widespread clinical use of these cardiotonic agents, there remains ongoing debate regarding their comparative efficacy and safety in the early postoperative period following CABG. Existing studies have reported conflicting

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results, and direct comparative data remain limited, particularly in real-world clinical settings. Therefore, a comprehensive evaluation of the hemodynamic and clinical effects of commonly used cardiotonic agents is essential to optimize postoperative management strategies[11].

The present study aimed to perform a detailed comparative analysis of dobutamine, milrinone, and levosimendan in patients developing myocardial dysfunction in the early postoperative period following coronary artery bypass grafting. By assessing their impact on cardiac output, metabolic parameters, and clinical outcomes, this study seeks to provide evidence-based guidance for the rational selection of cardiotonic therapy in this high-risk patient population.

## MATERIALS AND METHODS

### Study design and population

This prospective observational study was conducted in a tertiary cardiac surgery center and included adult patients who underwent elective coronary artery bypass grafting (CABG) with the use of cardiopulmonary bypass. The study period covered patients operated on between 2022 and 2025. A total of 180 patients aged between 45 and 75 years were enrolled in the study.

All included patients developed low cardiac output syndrome (LCOS) within the first 6 hours after surgery, defined by reduced cardiac performance requiring pharmacological inotropic support. LCOS diagnosis was based on a combination of clinical, hemodynamic, and laboratory criteria, including hypotension, reduced cardiac index, low urine output, elevated serum lactate levels, and echocardiographic evidence of impaired left ventricular systolic function.

### Inclusion criteria

Patients were eligible for inclusion if they met all of the following criteria:

- Left ventricular ejection fraction (LVEF) ≤ 45% documented by transthoracic echocardiography in the early postoperative period
- Clinical and hemodynamic requirement for cardiotonic (inotropic) support due to signs of low cardiac output

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- Elective nature of the CABG procedure with the use of cardiopulmonary bypass
- Provision of written informed consent prior to participation in the study

**Exclusion criteria**

Patients were excluded from the study if any of the following conditions were present:

- Preoperative cardiogenic shock or requirement for mechanical circulatory support before surgery
- Severe concomitant valvular heart disease requiring surgical correction
- Chronic renal failure with estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 $m^2$
- Known hypersensitivity or contraindications to any of the study drugs
- Significant arrhythmias requiring immediate antiarrhythmic intervention

**Intervention and group allocation**

After the diagnosis of LCOS in the early postoperative period, patients were allocated into three equal groups (n = 60 in each group) according to the cardiotonic agent administered as part of standard clinical management. Allocation was based on the treating physician's decision and institutional protocols.

- **Group D (Dobutamine group):** Patients received continuous intravenous infusion of dobutamine at a dose of 5–10 µg/kg/min, titrated according to hemodynamic response and clinical condition.
- **Group M (Milrinone group):** Patients were treated with milrinone administered as a continuous intravenous infusion at a dose of 0.375–0.75 µg/kg/min without a loading dose, with careful monitoring of blood pressure and renal function.
- **Group L (Levosimendan group):** Patients received levosimendan starting with a loading dose of 12 µg/kg administered over 10 minutes, followed by a continuous infusion at a rate of 0.1 µg/kg/min for 24 hours.

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All patients received standard postoperative care, including mechanical ventilation, fluid management, vasopressor support if required, and routine intensive care monitoring.

**Outcome measures**

The primary outcome measures were changes in left ventricular systolic function and global cardiac performance within the first 48 hours after surgery. These included:

- Left ventricular ejection fraction (LVEF), assessed by transthoracic echocardiography
- Cardiac index (CI), measured using invasive or non-invasive hemodynamic monitoring techniques

**Secondary outcome measures included:**

- Serum lactate levels as a marker of tissue perfusion and metabolic status
- Duration of intensive care unit (ICU) stay
- Incidence of postoperative heart failure requiring escalation of therapy
- In-hospital mortality

**Statistical analysis**

Statistical analysis was performed using **SPSS software version 26.0**. Continuous variables were tested for normal distribution and expressed as mean ± standard deviation. Comparisons between the three study groups were performed using one-way analysis of variance (ANOVA). When statistically significant differences were identified, post-hoc Tukey testing was applied for pairwise comparisons.

Categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate. A p-value of less than 0.05 was considered statistically significant for all analyses.

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## RESULTS

### Baseline characteristics

Baseline demographic and clinical characteristics were comparable among the three study groups. There were no statistically significant differences with regard to age, sex distribution, body mass index, prevalence of diabetes mellitus, hypertension, or smoking status. Preoperative left ventricular ejection fraction, number of bypass grafts performed, duration of cardiopulmonary bypass, and aortic cross-clamp time were also similar across all groups. These findings indicate that the study population was well balanced and that subsequent differences in outcomes were unlikely to be influenced by baseline confounding factors.

### Primary outcomes

At 48 hours following CABG, patients treated with levosimendan demonstrated a significantly greater improvement in left ventricular systolic function compared with the other two groups. Mean LVEF increased markedly in the levosimendan group, whereas only moderate improvement was observed in the milrinone group and a comparatively limited increase was noted in the dobutamine group. The differences between the levosimendan group and both comparator groups reached statistical significance ($p < 0.05$).

Similarly, cardiac index increased significantly in all three groups following initiation of cardiotonic therapy; however, the magnitude of improvement was highest in the levosimendan group. Patients receiving levosimendan achieved earlier and more sustained normalization of cardiac index values, suggesting superior hemodynamic stabilization during the early postoperative period. In contrast, increases in cardiac index in the dobutamine and milrinone groups were less pronounced and more variable.

### Secondary outcomes

Serum lactate levels, used as a surrogate marker of tissue perfusion and metabolic recovery, decreased progressively in all groups during the first 48 postoperative hours. Notably, the reduction in lactate concentration was significantly faster and

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more pronounced in the levosimendan group. This finding reflects more effective restoration of systemic perfusion and improved microcirculatory function in these patients. In comparison, lactate clearance was slower in the milrinone group and least favorable in the dobutamine group.

The incidence of postoperative heart failure differed significantly among the three treatment strategies. Patients treated with levosimendan exhibited the lowest rate of postoperative heart failure (10%), followed by the milrinone group (18%), while the highest incidence was observed in patients receiving dobutamine (28%). These differences were statistically significant and clinically relevant, indicating a potential protective effect of levosimendan against the progression of myocardial dysfunction.

Length of intensive care unit (ICU) stay was significantly shorter in patients treated with levosimendan. Earlier hemodynamic stabilization and improved cardiac performance in this group translated into faster weaning from mechanical ventilation and reduced need for prolonged intensive care monitoring. Patients in the milrinone group demonstrated intermediate ICU lengths of stay, whereas those receiving dobutamine required the longest ICU support.

In-hospital mortality was numerically lower in the levosimendan group compared with the milrinone and dobutamine groups; however, due to the limited number of events, this difference did not reach statistical significance.

**Summary of key findings**

Overall, levosimendan therapy was associated with superior improvement in left ventricular function, more effective enhancement of cardiac output, faster normalization of metabolic parameters, lower incidence of postoperative heart failure, and reduced ICU length of stay when compared with milrinone and dobutamine in patients with low cardiac output syndrome following CABG.

## DISCUSSION

The findings of the present study demonstrate that levosimendan provides superior myocardial support in the early postoperative period following coronary artery bypass grafting (CABG) when compared with dobutamine and milrinone.

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The observed improvements in left ventricular ejection fraction, cardiac index, metabolic recovery, and clinical outcomes highlight the potential advantages of levosimendan in the management of low cardiac output syndrome (LCOS) after cardiac surgery.

One of the most important mechanisms underlying the beneficial effects of levosimendan is its unique mode of action as a calcium sensitizer. By enhancing the sensitivity of cardiac troponin C to intracellular calcium, levosimendan improves myocardial contractility without increasing intracellular calcium concentration or myocardial oxygen consumption. This pharmacological profile is particularly advantageous in the setting of ischemic or stunned myocardium, which is commonly encountered in the early postoperative period after CABG. In contrast, β-adrenergic agonists such as dobutamine increase myocardial oxygen demand and may exacerbate ischemia, especially in patients with incomplete revascularization or residual coronary stenosis.

In addition to its inotropic properties, levosimendan exerts vasodilatory effects through the opening of adenosine triphosphate-dependent potassium channels in vascular smooth muscle cells. This results in reduced preload and afterload, improved coronary blood flow, and enhanced microcirculatory perfusion. These effects likely explain the faster reduction in serum lactate levels observed in the levosimendan group, reflecting improved systemic perfusion and metabolic recovery. Improved lactate clearance has been consistently associated with better postoperative outcomes and reduced mortality in cardiac surgery patients.

Compared with milrinone, levosimendan demonstrated superior hemodynamic stability in the present study. Although milrinone also provides inotropic support and reduces afterload via phosphodiesterase-III inhibition, its vasodilatory effect may lead to systemic hypotension and increased vasopressor requirements. Such hemodynamic instability can offset the beneficial effects of improved contractility and may prolong intensive care unit (ICU) stay. In contrast, levosimendan was associated with more stable blood pressure profiles and earlier achievement of hemodynamic targets, contributing to shorter ICU length of stay.

The significantly lower incidence of postoperative heart failure observed in patients receiving levosimendan represents a clinically meaningful finding.

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Postoperative heart failure remains one of the most serious complications following CABG and is associated with prolonged hospitalization, increased resource utilization, and higher mortality. The reduction in heart failure incidence in the levosimendan group suggests not only short-term hemodynamic benefits but also potential protective effects on myocardial function. This may be partly attributable to levosimendan's anti-ischemic, anti-stunning, and mitochondrial protective properties, which may facilitate myocardial recovery beyond the immediate postoperative period.

The results of the present study are consistent with previously published randomized controlled trials and meta-analyses evaluating levosimendan in cardiac surgery populations. Several studies have reported improved cardiac performance, reduced need for additional inotropic or mechanical support, and shorter ICU stays in patients treated with levosimendan, particularly among those with pre-existing left ventricular dysfunction. However, it should be noted that some studies have reported neutral effects on mortality, highlighting the complexity of patient selection and timing of administration.

Despite the encouraging findings, several limitations of the present study should be acknowledged. The observational design and single-center setting may limit the generalizability of the results. In addition, long-term outcomes beyond the in-hospital period were not assessed, and therefore the impact of levosimendan on long-term survival and functional recovery remains uncertain. Furthermore, although baseline characteristics were comparable among groups, unmeasured confounding factors cannot be completely excluded.

The reduction in postoperative heart failure incidence observed in the levosimendan group suggests potential long-term benefits; however, further large-scale, multicenter randomized controlled trials with extended follow-up are required to confirm these findings and to define optimal patient selection criteria, dosing strategies, and timing of administration. Future studies should also explore the cost-effectiveness of levosimendan therapy in comparison with conventional inotropic agents in the context of modern cardiac surgical practice.

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## LIMITATIONS

This study has several limitations, including its single-center design and lack of long-term outcome assessment. Additionally, the study was not randomized, which may introduce selection bias.

## CONCLUSION

The findings of the present study indicate that levosimendan is more effective than dobutamine and milrinone in improving myocardial function and achieving favorable early clinical outcomes in patients undergoing coronary artery bypass grafting complicated by low cardiac output syndrome. Levosimendan therapy was associated with greater improvement in left ventricular systolic performance, more pronounced enhancement of cardiac index, faster metabolic recovery as reflected by improved lactate clearance, and a lower incidence of postoperative heart failure.

Importantly, the use of levosimendan resulted in improved hemodynamic stability and a significant reduction in intensive care unit length of stay, suggesting a meaningful impact on postoperative recovery and resource utilization. These benefits are likely attributable to its unique mechanism of action as a calcium sensitizer, which enhances myocardial contractility without increasing myocardial oxygen demand, thereby providing effective support in the setting of ischemic or stunned myocardium.

Based on these findings, levosimendan appears to be a valuable therapeutic option for patients at high risk of developing postoperative low cardiac output syndrome after CABG, particularly those with pre-existing left ventricular dysfunction. Its routine or early targeted use in selected high-risk patients may contribute to improved postoperative recovery, reduced ICU burden, and optimization of perioperative management strategies.

Nevertheless, further large-scale, multicenter randomized controlled trials with long-term follow-up are warranted to confirm these results, evaluate long-term survival and functional outcomes, and establish standardized protocols for the optimal use of levosimendan in contemporary cardiac surgical practice.

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## ETHICAL CONSIDERATIONS

The study protocol was approved by the local ethics committee. Written informed consent was obtained from all participants.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## FUNDING

No external funding was received.

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