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Research Article

Effect of Intraoperative Milrinone on Left Ventricular Diastolic Function Patients Undergoing CABG: A Transesophageal Echocardiography Study

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Abstract

Introduction: This study evaluated whether intraoperative milrinone improves cardiac diastolic and systolic function in patients undergoing elective on-pump CABG.

Method: In this prospective study, 30 patients undergoing elective on-pump CABG were allocated equally to a milrinone group (n=15) or a control group (n=15). After anesthesia induction and before CPB, the milrinone group received a loading dose of 50 µg/kg over 10 minutes, followed by an infusion of 0.5 µg/kg/min continued for 6 hours postoperatively; the control group received an identical volume of normal saline. TEE was performed at two time points: after induction (baseline) and after separation from CPB. Baseline diastolic function was characterized using standard Doppler indices; however, patients were not preselected or stratified by diastolic dysfunction grade, which represents a limitation of the study design. Echocardiographic indices (fractional area change [FAC], pulmonary venous flow velocity [PV], deceleration time [DT], E/PV, A-wave duration [Adur], atrial reversal duration [ARdur]), hemodynamic variables, vasoactive requirements, and intensive care unit (ICU) length of stay were compared between groups.

Result: Baseline characteristics, including age, sex, weight, height, comorbidities, left ventricular ejection fraction (p=0.10), surgical duration (p=0.18), and CPB duration (p=0.10) were comparable between groups. Milrinone significantly increased FAC after CPB relative to control (55.39±10.86% vs 45.71±12.04%; p=0.028) and relative to its own baseline (vs 42.77±11.27%; p<0.001). Pulmonary venous flow velocity after CPB was significantly higher in the milrinone group than in controls (96.95±31.08 vs 76.03±22.54 cm/s; p=0.049) and higher than its own baseline (vs 63.59±20.72 cm/s; p<0.001). No significant between-group differences were observed in DT, E/PV, Adur, or ARdur. Hemodynamic parameters, norepinephrine requirement during CPB (p=0.92), inotrope and nitroglycerin dosing, cardiac rhythm, and ICU length of stay did not differ significantly between groups

Conclusion : Intraoperative milrinone significantly improved systolic performance (FAC) and pulmonary venous flow in patients undergoing elective on-pump CABG, with a relative improvement in selected diastolic indices and no adverse hemodynamic effects. However, because patients were not preselected for baseline diastolic dysfunction, the study was underpowered to detect a dedicated diastolic benefit. These findings suggest a potential role for milrinone in the perioperative management of CABG patients, particularly those with preexisting diastolic dysfunction. Adequately powered multicenter trials are warranted to confirm a dedicated diastolic benefit and to evaluate its impact on clinical outcomes, particularly in higher-risk or critically ill subpopulations.

Keywords: Milrinone; Diastolic dysfunction; Transesophageal echocardiography; Coronary artery bypass grafting; Cardiopulmonary bypass; Phosphodiesterase-3 inhibitor.

Introduction

Cardiovascular disease remains the leading cause of death worldwide, accounting for roughly one-third of global mortality, with coronary artery disease representing the principal indication for coronary artery

bypass grafting (CABG) [1]. Despite significant advances in surgical techniques and perioperative care, the management of critically ill patients during separation from cardiopulmonary bypass (CPB) and the prevention of postoperative low cardiac output syndrome continue to pose substantial challenges in the cardiac intensive care unit (ICU) [2].

Left ventricular diastolic dysfunction is the most frequent echocardiographic abnormality detected in patients with unstable hemodynamics following open-heart surgery and has been identified as an independent predictor of difficult weaning from CPB, prolonged ICU stay, and adverse postoperative outcomes [2,3]. Left ventricular diastolic dysfunction is an underestimated disease with a high risk for acute decompensation in the perioperative period [3]. Severe diastolic dysfunction is reported as the most important determinant of postoperative outcome after cardiac surgery [4]. In a large cohort of patients undergoing CABG surgery, more advanced grades of diastolic dysfunction, as determined intraoperatively by transesophageal echocardiography (TEE), were associated with an increased risk of major adverse cardiac events [5]. Additionally, elevated left ventricular end-diastolic pressure, as a marker of moderate or severe diastolic dysfunction, is an independent predictor of postoperative morbidity and mortality after surgical coronary revascularization, irrespective of left ventricular ejection fraction [6]. While systolic function has historically dominated perioperative assessment, contemporary evidence increasingly underscores the prognostic significance of diastolic impairment in the critically ill surgical population. Updated echocardiographic guidelines now provide a structured framework for its intraoperative evaluation, facilitating timely identification of high-risk patients [7].

Milrinone, a selective phosphodiesterase-3 inhibitor, increases intracellular cyclic adenosine monophosphate, producing positive inotropy, peripheral and pulmonary vasodilation, and enhanced myocardial relaxation (lusitropy)—actions that are mechanistically independent of its inotropic effect [8]. These pharmacological properties render milrinone a theoretically attractive agent for the perioperative management of critically ill CABG patients, particularly those with preexisting diastolic dysfunction [9]. Prior randomized studies in cardiac surgical populations have demonstrated favorable hemodynamic profiles and short-term outcomes with milrinone; however, most investigations have emphasized systolic indices, hemodynamic stability, or composite clinical endpoints. Relatively few studies have quantified diastolic function intraoperatively using transesophageal echocardiography (TEE), and none have specifically examined this relationship in the context of critical care management following CABG [9,10]. A prospective randomized study in CABG patients found that milrinone administered after aortic declamping significantly improved left ventricular active relaxation, as assessed by acoustic quantification and peak filling rate [11]. However, a subsequent study in 50 patients undergoing CABG reported that prophylactic milrinone improved systolic function but was not associated with improved biventricular diastolic function [12]. This discrepancy underscores the need for further investigation. These guidelines emphasize the importance of a comprehensive diastolic assessment that integrates multiple parameters, including transmitral inflow velocities (E, A, E/A ratio, deceleration time), pulmonary venous flow, tissue Doppler imaging (septal and lateral e' velocities, E/e' ratio), left atrial volume index, and—more recently—left atrial strain [7,13]. Tissue Doppler imaging and left atrial strain are particularly valuable because they are less load-dependent than conventional Doppler parameters and provide more robust assessment of myocardial relaxation and filling pressures [13, 15].

TEE provides high-resolution, real-time intraoperative imaging that permits serial assessment of systolic and diastolic parameters during CPB, making it an invaluable tool for guiding perioperative decision-making in the critically ill [12]. We therefore conducted a prospective study to evaluate the effect of intraoperative milrinone on left ventricular diastolic and systolic function, assessed by TEE, in high-risk patients undergoing elective on-pump CABG. We hypothesized that milrinone, administered before CPB and continued postoperatively, would improve TEE-derived indices of cardiac function without compromising hemodynamic stability or increasing vasoactive requirements, thereby potentially improving outcomes in this vulnerable critically ill population.

Methods

Study design and setting

This prospective study was conducted in the cardiac operating theatre of a tertiary referral hospital between May 2018 and May 2019. The institutional ethics committee approved the study protocol, and written informed consent was obtained from all participants before enrolment. The trial was performed in accordance with the Declaration of Helsinki.

Participants

Adult patients scheduled for elective, isolated, on-pump CABG were eligible. Patients were excluded if they had significant valvular disease, a contraindication to TEE (e.g., oesophageal pathology), emergency or redo surgery, or a known hypersensitivity to milrinone. Importantly, patients were not preselected or stratified according to baseline diastolic function grade. Consequently, the study population included patients across the spectrum of diastolic function—from normal to impaired—without enrichment for those with preexisting diastolic dysfunction. This design choice, while reflecting a pragmatic approach to patient enrollment, limits the ability to detect a dedicated lusitropic effect, as the potential benefit of milrinone would logically be greatest in patients with baseline diastolic impairment [3,4]. Thirty patients meeting the criteria were enrolled and randomly allocated in a 1:1 ratio to a milrinone (case) group or a control group, with 15 patients in each arm.

Anesthetic management and intervention

Anesthesia was induced and maintained according to the institutional standard for cardiac surgery, and all patients underwent on-pump CABG. After induction of anesthesia and before initiation of CPB, patients in the milrinone group received a loading dose of milrinone 50 µg/kg diluted in 200 mL of normal saline administered over 10 minutes, followed by a continuous infusion of 0.5 µg/kg/min delivered by syringe pump and continued for 6 hours after surgery. Patients in the control group received 200 mL of normal saline as a loading dose, followed by a normal-saline infusion administered in the same manner to preserve blinding.

Echocardiographic assessment

TEE was performed at two predefined time points: (i) after induction of anesthesia and before administration of the study drug or placebo (baseline), and (ii) after separation from CPB. These time points were selected to capture the acute intraoperative effect of milrinone during the critical period of weaning from CPB, when diastolic dysfunction is most clinically relevant [2,3]. Left ventricular end-diastolic area (EDA) and end-systolic area (ESA) were traced to derive fractional area change (FAC = EDA − ESA / EDA × 100).

Diastolic Assessment

Diastolic assessment included transmitral and pulmonary venous Doppler-derived indices:

Deceleration time (DT): Measured from the deceleration slope of the E-wave;

Peak pulmonary venous flow velocity (PV): Measured during systole;

E/PV ratio: Ratio of early transmitral inflow velocity to pulmonary venous flow velocity;

A-wave duration (Adur): Duration of the transmitral A-wave;

Atrial reversal duration (ARdur): Duration of the pulmonary venous atrial reversal wave.

An experienced operator obtained all measurements according to standard echocardiographic methodology and was blinded to group allocation.

Limitations of the Diastolic Assessment Protocol

We recognize that the diastolic assessment protocol has significant limitations:

1. Exclusive reliance on load-dependent parameters: All measured diastolic indices (DT, PV, E/PV, Adur, ARdur) are Doppler-derived parameters that are highly sensitive to changes in preload, afterload, heart rate, and contractility 13. These parameters reflect the composite effect of myocardial relaxation, left atrial pressure, and loading conditions, rather than intrinsic diastolic function alone.

2. Absence of contemporary load-independent parameters: The study did not incorporate tissue Doppler imaging (TDI), which is the recommended method for assessing myocardial relaxation velocity (e') and estimating left ventricular filling pressures (E/e' ratio) 7. TDI measurements—particularly septal and lateral e' velocities—are less load-dependent than

conventional Doppler parameters and provide a more reliable assessment of intrinsic myocardial relaxation [13,15].

3. Absence of left atrial assessment: Left atrial volume index (LAVI) and left atrial strain are recommended parameters for diastolic function assessment [7,17]. These parameters were not measured in the present study. Left atrial strain, in particular, has emerged as a sensitive marker of diastolic dysfunction and left ventricular filling pressure that is less influenced by acute loading conditions [17].

4. Inability to perform formal diastolic grading: Without tissue Doppler imaging, left atrial volume index, or left atrial strain, formal grading of diastolic dysfunction according to ASE/EACVI criteria 7 could not be performed. This prevents accurate characterization of the study population's baseline diastolic status and limits the ability to assess milrinone's effect across different grades of diastolic dysfunction.

5. Impact on interpretability: The exclusive reliance on load-dependent parameters is particularly problematic in the perioperative setting, where loading conditions change rapidly due to CPB-related volume shifts, vasoactive medication administration, and hemodynamic instability. As a result, the diastolic measurements obtained in this study cannot be interpreted as pure measures of milrinone's lusitropic effect; they reflect the integrated effect of the drug plus all concurrent physiological perturbations.

Rationale for the Chosen Parameters

Despite these limitations, the conventional Doppler parameters used in this study were selected for several practical reasons:

They were the standard parameters available in the clinical TEE setting at the time of study conduct;

They allow comparison with prior studies that have similarly used conventional Doppler indices to assess perioperative diastolic function [11,12];

They are feasible to obtain intraoperatively without prolonging the procedure or requiring additional specialized software.

However, we acknowledge that the absence of tissue Doppler imaging and left atrial strain represents a significant limitation that prevents definitive conclusions about milrinone's diastolic effects.

Outcomes and intraoperative monitoring

The primary outcomes were TEE-derived systolic and diastolic indices (FAC, PV, DT, E/PV, Adur, ARdur) compared between groups and between time points. Secondary outcomes included blood pressure, heart rate and central venous pressure (CVP) recorded from arrival in the operating room through 24 hours in the intensive care unit (ICU); the requirement for norepinephrine during CPB to maintain a mean arterial pressure of 50–80 mmHg; the need for inotropes, pacing and intra-aortic balloon pump at separation from CPB; and, in the ICU, the duration of admission and the requirement for nitroglycerin and inotropic agents to maintain systolic blood pressure between 100 and 140 mmHg. Surgical duration (operating-room entry to ICU transfer) and CPB duration were recorded.

Statistical analysis

Continuous variables are presented as mean ± standard deviation. Between-group comparisons were performed with the independent-samples t test for normally distributed continuous variables (assessed using the Shapiro–Wilk test) or the Mann–Whitney U test for non-normally distributed variables; within-group (baseline vs post-CPB) comparisons were performed with the paired-samples t test or Wilcoxon signed-rank test as appropriate. Categorical variables were compared with the chi-square test or Fisher exact test as appropriate. A two-sided p-value < 0.05 was considered statistically significant. Analyses were performed using standard statistical software (SPSS version 22.0).

Results

The two groups were well matched at baseline across all demographic, clinical, and perioperative variables (Table 1). Mean age was 59.93 ± 9.60 years in the control group and 61.93 ± 7.81 years in the milrinone group ($p = 0.53$). Sex distribution was similar between groups, with male patients comprising 73.3% (n=11) of the control group and 66.7% (n=10) of the milrinone group ($p = 0.69$). Mean weight (70.53 ± 7.99 vs 73.27 ± 10.67 kg; $p = 0.43$), height (165.06 ± 9.30 vs 166.86 ± 7.64 cm; $p = 0.56$), and BMI (25.89 ± 2.85 vs 26.28 ± 3.42 kg/m²; $p = 0.51$) did not differ significantly between groups.

Comorbidity prevalence was comparable between groups. Hypertension was present in 60.0% (n=9) of controls and 66.7% (n=10) of milrinone-treated patients

(p=0.70). Diabetes mellitus (40.0% vs 46.7%; p = 0.71), dyslipidemia (53.3% vs 60.0%; p = 0.72), previous myocardial infarction (33.3% vs 26.7%; p = 0.69), and previous PCI (20.0% vs 13.3%; p = 0.62) showed no significant between-group differences. Preoperative medication use was also balanced, with high rates of aspirin (93.3% vs 86.7%; p = 0.54), β-blockers (80.0% vs 73.3%; p = 0.67), ACE inhibitors/ARBs (66.7% vs 73.3%; p = 0.69), and statins (86.7% vs 93.3%; p = 0.54) in both groups (Table 1).

Preoperative LVEF was comparable between groups (48.07 ± 10.82% in controls vs 52.13 ± 9.24% in the milrinone group; p = 0.10). When categorized, LVEF ≤ 40% was observed in 20.0% (n=3) of controls and 13.3% (n=2) of milrinone patients (p = 0.62), LVEF 41–50% in 33.3% (n=5) vs 26.7% (n=4; p = 0.69), and LVEF > 50% in 46.7% (n=7) vs 60.0% (n=9; p = 0.47). Baseline diastolic parameters were also comparable between groups, as shown in Table 2.

Perioperative characteristics showed no significant differences. Surgical duration (215.67 ± 32.45 vs 223.53 ± 28.76 minutes; p = 0.18), CPB duration (78.53 ± 20.17 vs 85.07 ± 22.46 minutes; p = 0.10), aortic cross-clamp time (52.40 ± 15.32 vs 56.53 ± 17.81 minutes; p = 0.34), and number of grafts (2.87 ± 0.74 vs 3.07 ± 0.70; p = 0.39) were similar between groups. Intraoperative fluid and transfusion requirements did not differ significantly (Table 1).

We did not formally stratify patients by diastolic dysfunction grade at enrollment. The distribution of baseline diastolic function across the spectrum from normal to impaired was therefore not systematically characterized, and subgroup analysis based on baseline diastolic status was not performed. This represents a significant limitation, as discussed below.

Baseline Diastolic Function

Baseline diastolic parameters are presented in Table 2. Deceleration time was 212.36 ± 79.91 ms in the control group and 209.61 ± 85.08 ms in the milrinone group (p = 0.92). E/PV ratio was 0.97 ± 0.40 vs 1.03 ± 0.42 (p = 0.67). A-wave duration was 139.28 ± 30.22 ms vs 143.06 ± 28.82 ms (p = 0.73), and atrial reversal duration was 105.0 ± 34.18 ms vs 94.26 ± 37.86 ms (p = 0.42). Peak pulmonary venous flow velocity showed a borderline between-group difference at baseline (86.79 ± 39.14 vs 63.59 ± 20.72 cm/s; p = 0.054).

Echocardiographic outcomes

At baseline, FAC did not differ between groups (42.77 ± 11.27% in the milrinone group vs 41.19 ± 13.54% in controls; p = 0.73). After separation from CPB, FAC was significantly higher in the milrinone group than in controls (55.39 ± 10.86% vs 45.71 ± 12.04%; p = 0.028). Within the milrinone group, FAC rose significantly from baseline to post-CPB (42.77 ± 11.27% to 55.39 ± 10.86%; p < 0.001).

Peak pulmonary venous flow velocity (PV) showed a borderline between-group difference at baseline (p = 0.054). After CPB, PV was significantly higher in the milrinone group than in controls (96.95 ± 31.08 vs 76.03 ± 22.54 cm/s; p = 0.049), and within the milrinone group, PV increased significantly from baseline (63.59 ± 20.72 cm/s) to post-CPB (96.95 ± 31.08 cm/s; p < 0.001).

Deceleration time (DT) did not differ significantly between groups at baseline (p = 0.92) or after CPB (p = 0.52). Similarly, E/PV (baseline p = 0.67; post-CPB p = 0.45), A-wave duration (baseline p = 0.73; post-CPB p = 0.20), and atrial reversal duration (baseline p = 0.42; post-CPB p = 0.22) showed no significant between-group differences at either time point (Table 2). A parameter-by-parameter comparison of the diastolic and systolic indices after separation from CPB is shown in Figure 1, and the within-group change in the milrinone arm from baseline to post-CPB is shown in Figure 2; the E/PV ratio is presented separately in Figure 3.

Hemodynamic and clinical outcomes

No significant between-group differences were observed in blood pressure, heart rate, or CVP at any of the recorded surgical stages or during the first 24 hours in the ICU. The requirement for norepinephrine during CPB did not differ between groups (p = 0.92). In the ICU, the mean dose of inotropic agents and nitroglycerin, changes in blood pressure and heart rate, and cardiac rhythm were comparable between groups. No adverse events attributable to milrinone were recorded.

Table 1. Baseline demographic, clinical, and perioperative characteristics of the study groups.

Variable	Control (n=15)	Milrinone (n=15)	p value
Demographics			
Age (years)	59.93 ± 9.60	61.93 ± 7.81	0.53
Male sex, n (%)	11 (73.3)	10 (66.7)	0.69
Weight (kg)	70.53 ± 7.99	73.27 ± 10.67	0.43
Height (cm)	165.06 ± 9.30	166.86 ± 7.64	0.56
BMI (kg/m²)	25.89 ± 2.85	26.28 ± 3.42	0.51
Comorbidities, n (%)			
Hypertension	9 (60.0)	10 (66.7)	0.70
Diabetes mellitus	6 (40.0)	7 (46.7)	0.71
Dyslipidemia	8 (53.3)	9 (60.0)	0.72
Previous MI	5 (33.3)	4 (26.7)	0.69
Previous PCI	3 (20.0)	2 (13.3)	0.62
Peripheral vascular disease	2 (13.3)	1 (6.7)	0.54
COPD	2 (13.3)	3 (20.0)	0.62
Chronic kidney disease	1 (6.7)	2 (13.3)	0.54
Preoperative Medications, n (%)			
Aspirin	14 (93.3)	13 (86.7)	0.54
Clopidogrel	5 (33.3)	4 (26.7)	0.69
β-blockers	12 (80.0)	11 (73.3)	0.67
ACE inhibitors/ARBs	10 (66.7)	11 (73.3)	0.69
Statins	13 (86.7)	14 (93.3)	0.54
Calcium channel blockers	4 (26.7)	3 (20.0)	0.67
Diuretics	5 (33.3)	6 (40.0)	0.71
Nitrates	7 (46.7)	6 (40.0)	0.72
Preoperative Cardiac Function			
LVEF (%)	48.07 ± 10.82	52.13 ± 9.24	0.10
LVEF ≤ 40%, n (%)	3 (20.0)	2 (13.3)	0.62
LVEF 41–50%, n (%)	5 (33.3)	4 (26.7)	0.69
LVEF > 50%, n (%)	7 (46.7)	9 (60.0)	0.47
Diastolic Function Parameters at Baseline			
E/A ratio	0.84 ± 0.31	0.87 ± 0.28	0.68
Deceleration time (ms)	212.36 ± 79.91	209.61 ± 85.08	0.92
E/e' ratio (if available)	—	—	—
Perioperative Characteristics			
Surgical duration (min)	215.67 ± 32.45	223.53 ± 28.76	0.18
CPB duration (min)	78.53 ± 20.17	85.07 ± 22.46	0.10
Aortic cross-clamp time (min)	52.40 ± 15.32	56.53 ± 17.81	0.34
Number of grafts	2.87 ± 0.74	3.07 ± 0.70	0.39
Intraoperative Variables			
Crystalloid volume (mL)	1850 ± 425	1920 ± 380	0.43
Colloid volume (mL)	650 ± 180	680 ± 165	0.52
RBC transfusion, n (%)	4 (26.7)	5 (33.3)	0.69
FFP transfusion, n (%)	2 (13.3)	1 (6.7)	0.54
Platelet transfusion, n (%)	1 (6.7)	2 (13.3)	0.54

Values are mean ± standard deviation or n (%) as appropriate. BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; LVEF, left ventricular ejection fraction; CPB, cardiopulmonary bypass; RBC, red blood cells; FFP, fresh frozen plasma. Dashes indicate parameter was not available in the dataset.

Table 2. Comparison of TEE-derived indices between groups at baseline and after separation from cardiopulmonary bypass.

Parameter	Time point	Control (n=15)	Milrinone (n=15)	p value
FAC (%)	Baseline	41.19 ± 13.54	42.77 ± 11.27	0.73
FAC (%)	Post-CPB	45.71 ± 12.04	55.39 ± 10.86	0.028
PV (cm/s)	Baseline	86.79 ± 39.14	63.59 ± 20.72	0.054
PV (cm/s)	Post-CPB	76.03 ± 22.54	96.95 ± 31.08	0.049
DT (ms)	Baseline	212.36 ± 79.91	209.61 ± 85.08	0.92
DT (ms)	Post-CPB	198.55 ± 73.73	181.53 ± 68.86	0.52
E/PV	Baseline	0.97 ± 0.40	1.03 ± 0.42	0.67
E/PV	Post-CPB	1.27 ± 0.48	1.09 ± 0.77	0.45
Adur (ms)	Baseline	139.28 ± 30.22	143.06 ± 28.82	0.73
Adur (ms)	Post-CPB	116.42 ± 12.47	127.73 ± 30.41	0.20
ARdur (ms)	Baseline	105.0 ± 34.18	94.26 ± 37.86	0.42
ARdur (ms)	Post-CPB	107.8 ± 31.67	93.73 ± 29.99	0.22

Values are mean ± standard deviation. TEE, transesophageal echocardiography; CPB, cardiopulmonary bypass; FAC, fractional area change; PV, peak pulmonary venous flow velocity; DT, deceleration time; E/PV, ratio of early transmitral inflow velocity to pulmonary venous flow velocity; Adur, A-wave duration; ARdur, atrial reversal duration.

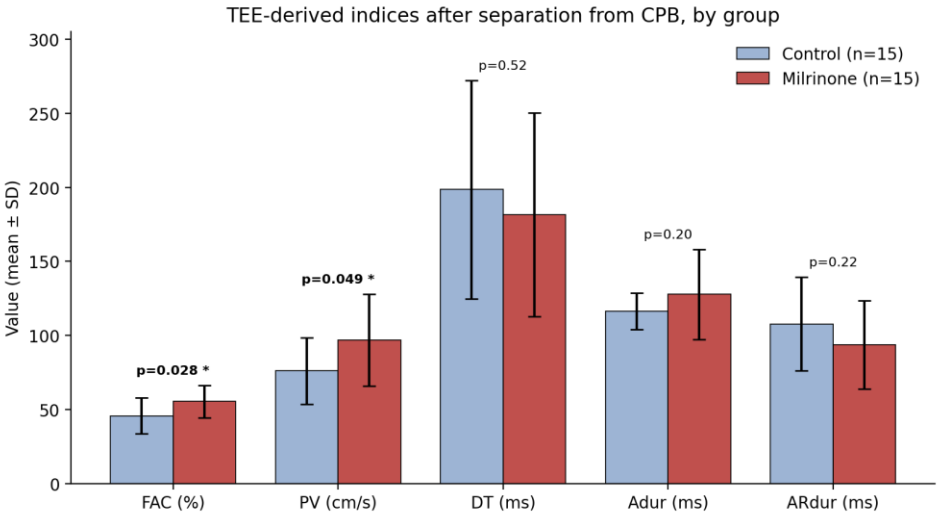

Figure 1. Comparison of echocardiographic parameters between control and milrinone groups after separation from cardiopulmonary bypass.

Bars represent mean ± standard deviation. FAC, fractional area changes; PV, peak pulmonary venous flow velocity; DT, deceleration time; Adur, A-wave duration; ARdur, atrial reversal duration. *p < 0.05 for between-group comparison (unadjusted).

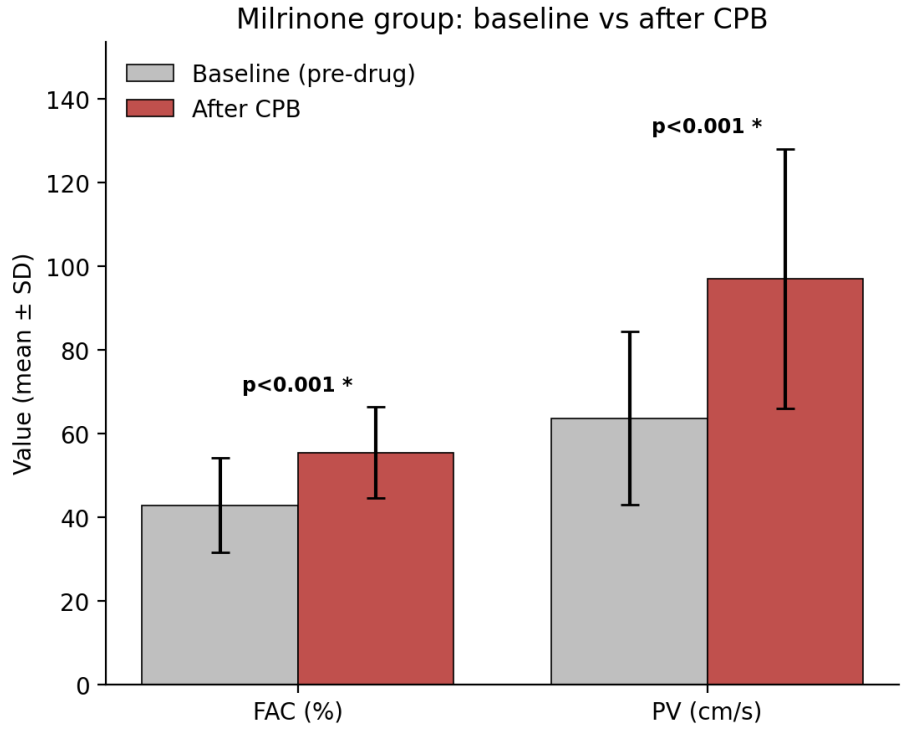

Figure 2. Changes in fractional area change (FAC) and pulmonary venous flow velocity (PV) from baseline to post-cardiopulmonary bypass in the milrinone group. Data are presented as mean ± standard deviation. Baseline measurements were obtained after anesthesia induction and before milrinone administration. Post-CPB measurements were obtained immediately after separation from cardiopulmonary bypass. †$p < 0.001$ versus baseline (paired t-test).

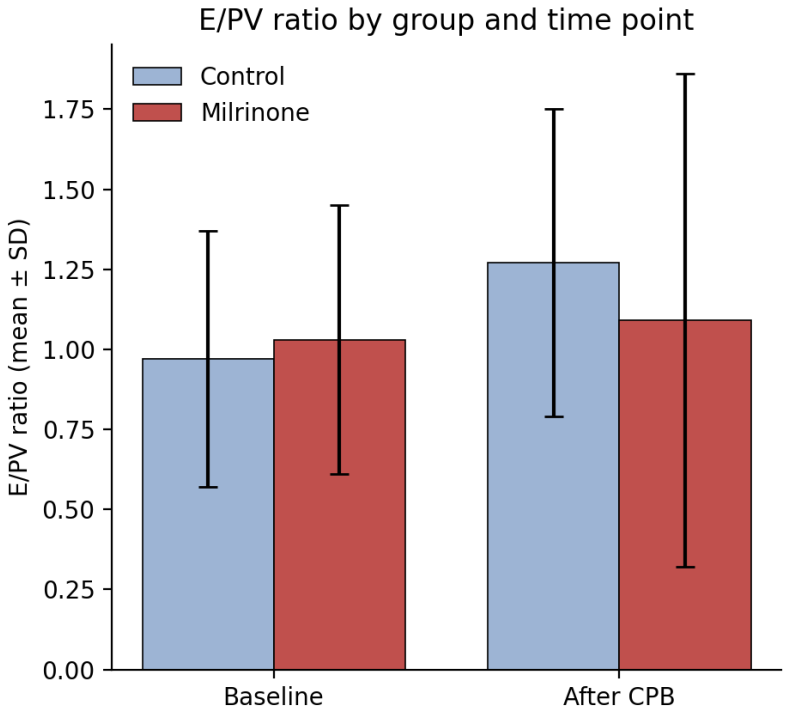

Figure 3. E/PV ratio by group and time point. E/PV, ratio of early transmitral inflow velocity to pulmonary venous flow velocity. Data are presented as mean ± standard deviation. Baseline: after anesthesia induction; Post-CPB: after separation from cardiopulmonary bypass. No significant between-group differences were observed at either time point ($p > 0.05$ for both).

Discussion

In this study, patients undergoing elective on-pump CABG received milrinone intraoperatively—before institution of cardiopulmonary bypass—and the infusion was deliberately continued for 6 hours into the early postoperative period. Hence, exposure spanned both separation from CPB and the vulnerable early recovery phase. Intraoperative milrinone significantly improved systolic performance, as reflected by a higher fractional area change after CPB relative to placebo and relative to baseline, and significantly increased pulmonary venous flow velocity. By contrast, the conventional diastolic indices that we measured—deceleration time, E/PV, A-wave duration, and atrial reversal duration—did not differ significantly between groups. Importantly, these benefits were achieved without deterioration in hemodynamic stability or increased vasoactive requirements, supporting the regimen's perioperative safety.

Our finding of a robust systolic improvement is consistent with the established inotropic profile of milrinone and with prior randomized and meta-analytic data in cardiac surgery. A systematic review and meta-analysis with trial sequential analysis of randomized trials in CABG patients reported that milrinone reduced myocardial infarction, myocardial ischemia, and arrhythmia. However, it did not reduce mortality 6. A broader network meta-analysis of inotropic agents in cardiac surgery similarly positioned milrinone among the agents improving cardiac performance, while ranking levosimendan most favorably for mortality and renal outcomes [7]. Our intraoperative, TEE-based demonstration of improved FAC complements these clinical-endpoint data by providing a direct echocardiographic correlate of the inotropic effect at the time of separation from CPB.

The increase in pulmonary venous flow velocity that we observed merits careful interpretation. Pulmonary venous Doppler is load- and rhythm-dependent and is influenced by both left atrial function and left ventricular filling. The concurrent rise in systolic ejection fraction (FAC) suggests that the higher pulmonary venous velocities in the milrinone group are most plausibly explained by enhanced overall cardiac performance and improved forward flow rather than by an isolated change in intrinsic relaxation. This interpretation aligns with the dual inotropic–lusitropic mechanism of phosphodiesterase-3 inhibition, in which augmented contractility and improved relaxation frequently coexist.[۵]

However, the absence of formal baseline diastolic function grading according to ASE/EACVI criteria 7 represents a critical limitation in interpreting these findings as evidence of improved diastolic function. Without prospective stratification by baseline diastolic impairment, the study population likely included a mixture of patients with normal diastolic function, grade I (impaired relaxation), and more advanced grades of dysfunction. The potential lusitropic benefit of milrinone would theoretically be most pronounced in patients with preexisting diastolic impairment [3,4]; inclusion of patients with normal diastolic function would dilute any detectable signal. This may explain, at least in part, why dedicated diastolic indices did not reach statistical significance in our analysis.

The absence of a statistically significant change in the dedicated diastolic indices is noteworthy and is best understood in light of several considerations, the most important of which is the exclusive reliance on load-dependent conventional Doppler parameters.

1. Fundamental Limitations of Load-Dependent Indices

All diastolic parameters measured in this study—deceleration time (DT), pulmonary venous flow velocity (PV), E/PV ratio, A-wave duration (Adur), and atrial reversal duration (ARdur)—are derived from conventional Doppler and are highly load-dependent [13]. These parameters reflect the integrated effect of: Myocardial relaxation (the intrinsic lusitropic property of the myocardium); Left atrial pressure (which is influenced by volume status and left ventricular compliance); Left ventricular compliance (which is affected by hypertrophy, ischemia, and fibrosis); Loading conditions (preload, afterload, heart rate, and contractility).

In the perioperative period, loading conditions change dramatically and rapidly. During CPB separation and the immediate post-bypass period: Volume status is highly variable, with large-volume crystalloid, colloid, and blood product administration; Vasoactive medications (norepinephrine, inotropes, vasodilators) are frequently adjusted to maintain hemodynamic targets; Heart rate and rhythm are often altered;

Temperature and anesthetic depth affect myocardial relaxation.

Consequently, changes in conventional Doppler parameters during this period cannot be attributed specifically to drug-induced lusitropy. A decrease in deceleration time, for example, could reflect improved relaxation, increased filling pressure, or both. Similarly, changes in pulmonary venous flow velocity could reflect improved left atrial function, reduced left ventricular filling pressure, or altered loading conditions.

2.The Need for Load-Independent Parameters

Contemporary guidelines [7,13] recommend incorporating tissue Doppler imaging (TDI) to provide a more load-independent assessment of diastolic function:

e' (early diastolic annular velocity): Reflects myocardial relaxation and is less load-dependent than conventional Doppler parameters [13];

E/e' ratio: Estimates left ventricular filling pressure and is a powerful predictor of outcomes [7];

Left atrial volume index (LAVI): Reflects chronic left ventricular filling pressure elevation [13];

Left atrial strain: A newer parameter that provides sensitive assessment of left atrial function and filling pressure, with emerging evidence supporting its value in diastolic dysfunction diagnosis [17].

In the present study, we did not measure any of these parameters. As a result, we could not distinguish between true lusitropic effects of milrinone and changes in loading conditions; We could not estimate left ventricular filling pressures (E/e') to assess whether milrinone reduced LVEDP; We could not perform formal diastolic grading according to ASE/EACVI criteria;

We could not determine whether the negative diastolic findings reflect a genuine absence of lusitropic activity or the use of inadequate parameters.

3. Comparison with Prior Literature

Prior studies demonstrating diastolic benefits of milrinone in cardiac surgery have used more robust assessment protocols. Axelsson et al. [11] used acoustic quantification and peak filling rate—parameters that, while still somewhat load-dependent, provide more direct assessment of ventricular filling dynamics than the conventional Doppler indices used in our study. More recent studies have incorporated tissue Doppler imaging to demonstrate milrinone's effects on e' and E/e' in various clinical settings.

The absence of TDI in our study represents a significant regression from contemporary standards and limits the comparability of our findings to the broader literature.

[4]. The Contrast Between Systolic and Diastolic Findings

The significant improvement in FAC (a systolic parameter that is less load-dependent) contrasts with the non-significant diastolic indices. This contrast may reflect:

A genuine predominance of milrinone's inotropic effect over its lusitropic effect in this population;

The greater load-dependence of the diastolic parameters obscuring a true lusitropic signal;

Inadequate diastolic assessment methodology failing to detect subtle changes in myocardial relaxation; The sample size being insufficient to detect modest diastolic changes while being adequate for the larger systolic effect.

We emphasize that the negative diastolic findings in this study cannot be interpreted as definitive evidence that milrinone lacks a diastolic benefit. Rather, they reflect the limitations of the measurement approach and the physiological complexity of the perioperative period. These results carry practical implications for cardiac anesthesia. Because diastolic dysfunction predicts difficult separation from CPB and worse postoperative outcomes [2,3], an agent that improves ventricular performance around the time of weaning without hemodynamic penalty is clinically attractive. Recent evidence on the route of administration is also relevant: a contemporary systematic review comparing intravenous and inhaled milrinone in cardiac surgery found broadly comparable pulmonary hemodynamic effects, with route-specific differences in systemic vascular resistance and filling pressures [8]. Our data, derived from intravenous administration, support the systemic functional benefit of this route. The role of milrinone should additionally be viewed within the evolving landscape of heart-failure pharmacotherapy, in which guideline-directed therapy for heart failure with preserved ejection fraction has expanded substantially [9]; however, milrinone remains a short-term perioperative

tool rather than a chronic therapy.

Standardized intraoperative assessment of diastolic function is central to translating these findings into practice. The most recent recommendations for the evaluation of left ventricular diastolic function by echocardiography refine the diagnostic algorithm and incorporate additional parameters—including tissue Doppler imaging (e'), left atrial volume index, and left atrial strain—to reduce indeterminate classifications [7]. Aligning intraoperative TEE protocols with this guidance is essential for future investigations. Most importantly, future trials must preselect and stratify patients according to baseline diastolic dysfunction grade to ensure adequate power to detect a dedicated lusitropic effect. Without such stratification, as shown in the present study, including patients with normal diastolic function may dilute any therapeutic signal and obscure genuine diastolic benefits.

Limitations

This study has several limitations. First, the single-center design and small sample size limit statistical power—particularly for the diastolic indices—and external generalizability.

Second, and most critically, patients were not preselected or stratified according to baseline diastolic function using the established ASE/EACVI grading criteria [7]. This represents a major methodological limitation because:

The study population likely included a heterogeneous mix of patients with normal diastolic function and various grades of diastolic impairment, diluting any potential lusitropic signal;

Subgroup analysis comparing milrinone's effect in patients with versus without preexisting diastolic dysfunction was not possible;

The absence of formal diastolic grading at baseline prevents accurate characterization of the population in whom milrinone's diastolic effects would be most relevant;

The negative findings for dedicated diastolic indices (DT, E/PV, Adur, ARdur) may reflect this dilution effect rather than a genuine absence of lusitropic activity.

Prior studies that have demonstrated milrinone's diastolic benefits, such as Axelsson et al. [11], specifically enrolled patients and characterized baseline diastolic function. The lack of such characterization in our study substantially limits our ability to conclude milrinone's effect on diastolic function specifically.

Third, diastolic assessment relied on load-dependent Doppler indices obtained at two time points under the dynamic conditions of cardiac surgery, and we did not use newer measures such as left atrial strain, tissue Doppler imaging (e' velocity), or the E/e' ratio. These contemporary parameters, recommended by updated guidelines [7], may have provided a more robust assessment of diastolic function. Fourth, our study population comprised hemodynamically stable patients undergoing elective surgery, not the broader or more heterogeneous "critically ill" population. Therefore, our findings are most directly generalizable to elective CABG patients without preoperative hemodynamic compromise. Fifth, the study was not powered for clinical endpoints such as mortality or major morbidity. These limitations should be addressed by adequately powered, multicentre trials that: Prospectively enroll patients with established diastolic dysfunction using formal ASE/EACVI grading criteria; Stratify randomization by baseline diastolic function grade; Employ contemporary diastolic assessment parameters including tissue Doppler and left atrial strain; Include higher-risk and critically ill subpopulations where the potential benefit of milrinone may be greatest.

Conclusion

In hemodynamically stable patients undergoing elective on-pump CABG, intraoperative milrinone significantly improved systolic function (FAC) and increased pulmonary venous flow velocity, with no adverse hemodynamic effects or increased vasoactive requirements. However, the exclusive reliance on conventional load-dependent Doppler parameters (DT, PV, E/PV, Adur, ARdur)—without contemporary load-independent measures such as tissue Doppler imaging (e', E/e' ratio), left atrial volume index, or left atrial strain—significantly limits the validity of the diastolic function assessment [7,13]. Changes in preload, afterload, heart rate, and contractility influence all measured diastolic indices, which vary substantially during the perioperative period. Consequently, the negative findings for these indices cannot be interpreted as definitive evidence that milrinone lacks a diastolic benefit; they may reflect the inadequacy of the measurement approach rather than a genuine absence of lusitropic activity. Additionally, the limited two-point assessment strategy and the lack of baseline diastolic

dysfunction characterization further constrain the interpretability of the diastolic findings.

These findings support a favorable intraoperative functional profile for milrinone in CABG patients, particularly regarding systolic performance, but underscore the critical need for adequately powered, multicentre trials that incorporate contemporary, load-independent diastolic parameters (tissue Doppler imaging, left atrial strain), employ serial echocardiographic assessments at multiple time points, and prospectively stratify by baseline diastolic function to definitively evaluate milrinone's diastolic effects.

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Conflict of Interest Disclosures

The authors declare that they have no competing interests.

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Authors' Contributions

All authors read and approved the final manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethical Statement

The study was approved by the institutional ethics committee, and written informed consent was obtained from all participants (IR.BMSU.REC.1398.030 code).

Declaration of Generative AI and AI-assisted technologies

The authors declare that the deep seek was used for language editing and paper analysis. However, all scientific content, expert analysis, data interpretation, and final conclusions were produced, reviewed, and verified directly by the authors.

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