# Milrinone Increases Flow in Coronary Artery Bypass Grafts After Cardiopulmonary Bypass: A Prospective, Randomized, Double-Blind, Placebo-Controlled Study

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***Objective:*** **To compare the effects of a bolus of milrinone, 50 μg/kg, versus placebo on flow in coronary artery bypass grafts after cardiopulmonary bypass (CPB).**

***Design:*** **A prospective, randomized, double-blind study.**

***Setting:*** **A university hospital.**

***Participants:*** **Forty-four patients with stable angina and left ventricular ejection fraction >30% scheduled for elective coronary artery bypass graft (CABG) surgery were included.**

***Intervention:*** **Patients were randomized to receive 50 μg/kg of milrinone (n = 22) or placebo (n = 22) after aortic declamping.**

***Measurements and Main Results:*** **The flow in coronary artery bypass grafts was measured with a transit time flow meter at 10 minutes and 30 minutes after termination of CPB. The hemodynamic evaluation included transesophageal echocardiography, mean arterial pressure (MAP), heart rate, and intracavitary measurement of left ventricular end-diastolic pressure (LVEDP). The flow in the saphenous vein grafts was significantly higher in the milrinone group when compared with the placebo group both at 10 and 30 minutes after termination of CPB ($p < 0.001$). At 10 minutes, the flow was 64.5 ± 37.4 mL/min (mean ± standard deviation) and 43.6 ± 25.7 mL/min in nonsequential vein grafts for milrinone and placebo, respectively. Corresponding values at 30 minutes were 54.8 ± 29.9 mL/min and 35.3 ± 22.4 mL/min. The left internal thoracic artery (LITA) flow was higher in the milrinone group but did not reach statistical significance. The fractional area change was higher, and the MAP and calculated pressure gradient (MAP-LVEDP) were lower at 10 minutes in the milrinone group.**

***Conclusion:*** **Milrinone significantly increases the flow in anastomosed saphenous vein grafts after CPB, and has beneficial effects on left ventricular function.**



***KEY WORDS: myocardial revascularization, CABG, coronary graft flow, chemicals and drugs, phosphodiesterase inhibitor, milrinone, transesophageal echocardiography***

MILRINONE AND OTHER PHOSPHODIESTERASE (PDE) III inhibitors have a positive inotropic effect by increasing the intramyocardial level of cyclic adenosine monophosphate.[1,2] There is also a general vasodilatation with a decrease in systemic vascular resistance and improved cardiac output without an increase in oxygen demand.[3-5] Milrinone has certain favorable effects that make it suitable for cardiac surgery, especially in patients with heart failure.[6,7] The saphenous vein is the most commonly used graft for coronary artery bypass graft (CABG) surgery. A correlation between graft flow and early patency rate in saphenous vein grafts (SVGs) has been shown.[8] To date, no studies have been published regarding the effect of milrinone on SVG flow. The aim of this study was to compare the effects of milrinone and placebo on flow in SVG after cardiopulmonary bypass, and the authors hypothesized that milrinone increases graft flow.

## METHODS

Forty-four patients scheduled to undergo isolated primary nonurgent CABG surgery were included during an 18-month period until May 2000. The same senior cardiac surgeon enrolled all participants. Ethical committee approval and written informed consent were obtained. Inclusion criteria were isolated CABG surgery, stable angina, left ventricular ejection fraction >30%, and sinus rhythm. The patients were randomized to a milrinone or a placebo group. All preoperative demographic data are shown in Table 1. The quality of the native coronary arteries was preoperatively graded according to the coronary angiography findings.

All patients were given a standardized premedication with intramuscular oxycodone and scopolamine (6.0-8.0 mg/0.3-0.4 mg) supplemented with oral flunitrazepam (1 mg). After the insertion of 2 peripheral intravenous catheters and a radial artery catheter, anesthesia was induced with thiopental and fentanyl (10 μg/kg). Intubation was facilitated with pancuronium (100 μg/kg). Anesthesia was maintained with an isoflurane/oxygen/air mixture supplemented with boluses of fentanyl (250 μg).

Cardiopulmonary bypass (CPB) was accomplished at moderate hypothermia (bladder temperature 30°-32°C) with nonpulsatile flow after systemic heparinization (bolus 300 U/kg body weight, target activated coagulation time >480 seconds). The bypass circuit was primed with 2,000 mL of Ringer's solution and 10,000 U of heparin. A membrane oxygenator was used in all patients. The aorta was cannulated with a DLP 22F cannula (Medtronic, Minneapolis, MN), and a 2-stage, single atrial cannula was inserted. Anterograde cardioplegia was delivered through an aortic root cannula, and the coronary sinus was cannulated for retrograde cardioplegia. After aortic cross-clamping, myocardial preservation was achieved with a combination of cold anterograde and retrograde blood cardioplegia and topical cooling. An initial anterograde cardioplegia bolus of 1,000 mL (potassium 20 mmol/L) was followed by a continuous retrograde flow of 50 mL/min (potassium 10 mmol/L) interrupted during suturing of the anastomoses. Once the patients had been rewarmed to normothermia and were in stable sinus rhythm, they were weaned from CPB. All patients were in sinus rhythm. Phenylephrine was used to keep the mean arterial pressure at a preset level (>50 mmHg). During weaning from CPB, no catecholamines were needed.

In all patients, the saphenous vein was dissected and manually distended by using a syringe of saline to prevent spasm and to control for possible leakage from side branches or dissection injuries of the wall. A senior member of the cardiac surgical team performed CABG

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**Table 1. Preoperative Data**

| Variable | Milrinone (n = 22) | Placebo (n = 22) |
|---|---|---|
| Age (y) | 63 (10) | 62 (9) |
| Sex (M/F) | 20/2 | 17/5 |
| Height (cm) | 176 (8) | 172 (8) |
| Weight (kg) | 83 (10) | 81 (15) |
| LVEF (%) | 59 (12) | 63 (9) |
| Diabetes (yes/no) | 3/19 | 7/15 |
| Aspirin | 22 | 19 |
| $\beta$-Receptor inhibitors | 18 | 21 |
| Nitrates | 16 | 17 |
| ACE inhibitors | 3 | 3 |
| Calcium channel inhibitors | 8 | 6 |
| Blood pressure (mmHg) | | |
| Systolic | 138 (17) | 137 (16) |
| Diastolic | 82 (9) | 76 (13) |
| MAP | 101 (9) | 97 (13) |

NOTE. Values are mean (standard deviation).

Abbreviations: LVEF, left ventricular ejection fraction; ACE, angiotensin-converting enzyme; MAP, mean arterial pressure.

surgery in a standard fashion. An aortic side clamp was applied to facilitate the suture of proximal anastomoses.

The patients were randomized to the respective groups by opening sealed envelopes outside the operating room during CPB. Nurses who did not participate in the study prepared the drugs. The patients in the milrinone group received a milrinone bolus of 50 $\mu$g/kg body weight, diluted in 0.9% NaCl to a total volume of 20 mL, over a 15-minute period without continued infusion. In the placebo group, only 20 mL of 0.9% NaCl were given during the same time period. The tube from the syringe pump was rinsed with 5 mL of 0.9% NaCl at the end of the drug administration. All drugs were delivered into the venous return of the CPB system after release of the aortic cross-clamp. The hemodynamic alterations during CPB were monitored and treated by the perfusionist with an infusion of phenylephrine to the preset level of mean arterial pressure. All persons involved in the operation and evaluation process were blinded to which group the patient had been assigned.

All patients were monitored with transesophageal echocardiography. The first consecutive 12 patients in each group had a transesophageal echocardiographic investigation by using a Sonos 2500 echo machine (Philips, Andover, MA) with an omniplane probe after the induction of anesthesia. The measurement was carried out using the acoustic quantification technique at 10 minutes after CPB.[9,10] Continuous recording of the area of the short axis of the left ventricle was computerized for later offline analysis. The fractional area change (FAC) was calculated from the end-diastolic area (EDA) and the end-systolic area (ESA) according to the following equation:

$$FAC = (EDA - ESA)/EDA$$

Hemodynamic data including heart rate and systolic, diastolic, and mean arterial pressure were recorded at 10 and 30 minutes after the termination of CPB. Left ventricular end-diastolic pressure was recorded at 10 minutes with a fluid-filled catheter. Graft flow measurements were performed at 10 and 30 minutes after the termination of CPB. The same transit time flowmeter (Transonic System Inc, Ithaca, NY) and 4-mm probes were calibrated and adjusted by the Department of Biomedical Engineering at the University Hospital and were used in all patients. The equipment has been investigated in a validation study by Lundell et al.[11] The complexity of the distribution of SVGs to the region of the left coronary bed led the authors to further analysis of the right coronary grafts as a standardized model of a regional myocardial perfusion area (Table 2). The fact that no sequential grafts and no arterial grafts were used to the right coronary artery made that assumption reasonable. In addition, the majority of the patients had grafts to the right coronary artery.

The power analysis and randomization were conducted by a statistician supported by a retrospective database analysis of flow measurements. The analysis of the differences in flow characteristics between the milrinone and the placebo groups was done with a multiple regression model that allowed for repeated measurements on the same graft (measurements both at 10 minutes and 30 minutes) as well as a potential dependence between grafts from the same patient. There were 272 measurements on 136 grafts for the 44 patients divided into 2 groups. Hence, the data should be regarded as observations with variations both at the graft level (SVG or left internal thoracic artery [LITA]) as well as the patient level (milrinone or placebo). The regression analysis was performed both for the whole material as well as stratified for venous or artery grafts. In the first analysis, a simultaneous test of the effect of treatment (milrinone *v* placebo), time (10 minutes *v* 30 minutes), and type of graft (venous nonsequential and venous sequential *v* artery) was performed; *p* values and estimates of the difference in flow (supplemented with 95% confidence intervals [CIs]) for the 3 factors, treatment, time, and type of graft, were calculated. In the stratified analysis, treatment and time differences were calculated, and, for venous grafts, the difference between sequential and nonsequential grafts was also calculated. The data from the sequential venous grafts could be handled in alternative ways. The flow measurements could be analyzed as such with no adjustment at all or adjusted to account for the fact that sequential grafting leads to a distribution of the measured total graft flow into each of the grafted coronary artery territories. Both alternatives were tested. In the adjustment method, the flow values were divided by 2 (or 3 in 1 patient), depending on the number of sequential anastomoses. However, a third alternative is reported here. In this approach, the authors distinguished between venous grafts of the nonsequential type and venous grafts of the sequential type, and, in the regression analysis, the authors were able to estimate the difference between these 2 types of grafts. The main reason for the choice of this method was to avoid the need for adjustment. From a statistical and scientific point of view, it seems more appropriate to evaluate actually measured values rather than estimated ones. The analysis was also done with restriction to only the right coronary nonsequential grafts. Because the assumption of normal distribution of flow could be questionable, the authors also analyzed the data after logarithmic transformation of flow. A *t* test was used in Tables 3 and 4 to compare differences of hemodynamic variables between the milrinone and placebo groups. A $p$ value $<0.05$ was considered statistically significant. The analyses were performed by

**Table 2. Perioperative Data**

| Variable | Milrinone (n = 22) | Placebo (n = 22) |
|---|---|---|
| Aortic cross-clamp (min) | 49 (14) | 54 (17) |
| Cardiopulmonary bypass (min) | 90 (26) | 94 (22) |
| Anterograde/retrograde cardioplegia (n) | 18/22 | 19/22 |
| Peripheral anastomoses | 76 | 78 |
| Saphenous vein grafts | 49 | 51 |
| Left internal thoracic artery | 22 | 14 |
| Left anterior descending artery | 22 | 14 |
| Diagonal branch | 14 | 12 |
| Circumflex artery | 9 | 11 |
| Intermediate artery | 5 | 0 |
| Right coronary artery | 16 | 20 |
| Sequential grafts | 5 | 14 |

NOTE. Values are mean (standard deviation).