Reports of Original Investigation

Milrinone enhances systolic, but not diastolic function during coronary artery bypass grafting surgery

[La milrinone améliore la fonction systolique mais non la fonction diastolique pendant la chirurgie de pontage aortocoronarien]

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Purpose: To evaluate the effect of milrinone on diastolic function during coronary artery bypass grafting surgery (CABG).

Methods: Fifty patients undergoing CABG were randomized to receive a bolus and infusion of milrinone or placebo before cardiopulmonary bypass (CPB) until skin closure. Hemodynamic and transesophageal echocardiographic measurements of systolic and diastolic function were obtained. Pulsed wave Doppler measurements of the early (E wave) and atrial components (A wave) of the transmitral (TMF) and transtricuspid (TTF) flows, and systolic (S wave), diastolic (D wave) and atrial components (Ar) of the pulmonary (PVF) and hepatic venous blood flow (HVF) velocities were performed. Early and atrial components of the mitral (Em and Am waves) and tricuspid annulus velocities (Et and At waves) were assessed by tissue Doppler imaging (TDI). Assessment of diastolic dysfunction was graded from normal to severe using a scale score.

Results: Cardiac index and heart rate were higher in the milrinone group compared to placebo after the administration of study drug (2.8 ± 0.6 *vs* 2.1 ± 0.5 $L \cdot min^{-1} m^{-2}$) ($P < 0.0001$) and (67 ± 8 *vs* 60 ± 12 $beats \cdot min^{-1}$) ($P < 0.05$) respectively. There were no changes in left and right ventricular diastolic dysfunction scores between study groups. Higher PVF S wave, HVF S wave, TTF A wave and At measured by TDI in the milrinone group compared with placebo suggested an improvement in ventricular systolic and atrial contraction.

Conclusion: Distinct from its effects on systolic function, milrinone administered before CPB is not with associated improved biventricular diastolic function in patients undergoing CABG.

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Objectif *: Evaluer l'effet de la milrinone sur la fonction diastolique durant un pontage aortocoronarien (PAC).*

Méthode *: Cinquante patients subissant un PAC ont été randomisés à recevoir soit une dose bolus et une perfusion de milrinone, soit un placebo avant la circulation extracorporelle (CEC) jusqu'à fermeture de la peau. Les mesures hémodynamiques et échocardiographiques transoesophagiennes des fonctions systolique et diastolique ont été obtenues. Les mesures Doppler pulsées des composantes précoces (onde E) et auriculaires (onde A) des débits transmitral (TMF) et transtricuspide (TTF), et les composantes systolique (onde S) diastolique (onde D) et auriculaires (Ar) des vélocités du débit sanguin veineux pulmonaire (PVF) et hépatique (HVF) ont été prises. Les composantes précoces et auriculaires des vélocités de l'anneau mitral (ondes Em et Am) et de l'anneau tricuspide (ondes Et et At) ont été mesurées par Doppler tissulaire (TDI). La dysfonction diastolique a été gradée de normale à sévère sur une échelle de scores.*

Résultats *: L'index cardiaque et la fréquence cardiaque ont été plus élevés dans le groupe milrinone comparé au groupe placebo après la prise du médicament à l'étude ($2,8 \pm 0,6$ vs $2,1 \pm 0,5$ $L \cdot min^{-1} m^{-2}$) ($P < 0,0001$) et (67 ± 8 vs 60 ± 12 $battements \cdot min^{-1}$) ($P < 0,05$), respectivement. Il n'y a pas eu de changement dans les résultats de scores de dysfonction diastolique des ventricules gauche et droit entre les groupes d'étude. On a mesuré par TDI*

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des ondes PVF S, HVF S et TTF A ainsi qu'un At plus élevés dans le groupe milrinone que dans le groupe placebo, ce qui suggère une amélioration de la contraction ventriculaire et auriculaire.

***Conclusion** : En dehors de ses effets sur la fonction systolique, la milrinone administrée avant la CEC n'est pas associée à une meilleure fonction diastolique biventriculaire chez les patients subissant un PAC.*

PREOPERATIVE left ventricular (LV) diastolic dysfunction appears to be a stronger predictor of hemodynamic instability after cardiopulmonary bypass (CPB) compared to systolic dysfunction[1] and more severe diastolic dysfunction present before cardiac surgery is associated with difficult separation from CPB.[2] Moreover, the presence of LV diastolic dysfunction has been shown to be an independent predictor of cardiac events (cardiac death, repeat hospital admission for congestive heart failure or myocardial infarction, and angina pectoris) at one year after coronary artery bypass graft (CABG) surgery.[3] This is clinically important because the prevalence of diastolic dysfunction in elderly and hypertensive patients undergoing cardiac surgery has been estimated to be 30%.[1] There are few data, however, assessing the influence of right ventricular diastolic function on patient outcomes after CABG surgery. We have previously observed that both left and right ventricular diastolic abnormalities were the most common echocardiographic findings in hemodynamically unstable patients after cardiac surgery,[4] and preoperative right ventricular diastolic dysfunction was associated with increased need for vasoactive drug support after surgery.[2,5] Because preoperative left and right ventricular diastolic dysfunction are associated with post-CPB hemodynamic instability, improvement of LV diastolic function could represent an approach to reduce the risk of instability following cardiac surgery.

Phosphodiesterase inhibitors such as milrinone increase cardiac output following CPB by inotropic and vasodilatory effects.[6–13] In addition, milrinone has been shown to improve diastolic performance in patients with congestive heart failure.[14] However, other studies evaluating the effects of milrinone on diastolic dysfunction have had contradictory results.[10,15,16] Some of these studies were conducted in the post-CPB setting and could not assess the independent response to milrinone because of the potential confounding effects of CPB and CABG. Therefore, the purpose of this study was to evaluate the effect of milrinone administered before CPB on left and right ventricular diastolic function in patients with pre-existing diastolic dysfunction undergoing CABG.

Methods

Following approval from the Research and Ethics Committee of the Montreal Heart Institute and after obtaining individual informed consent, consecutive patients undergoing CABG surgery under CPB were screened for LV diastolic dysfunction as determined by preoperative transthoracic echocardiographic examination performed on the day before surgery. The diagnostic criteria used to define left and right diastolic dysfunction are shown in Figures 1 and 2. Patients with mitral and aortic valvular disease, atrial fibrillation or pacemaker, and contraindication to transesophageal echocardiography (TEE) were excluded. Preoperative data collection included demographic information, presence of co-morbid conditions, preoperative medications, and the results of routine laboratory screening tests.

Eligible patients were randomized according to a computer-generated randomization sequence to receive either milrinone or normal saline placebo. Allocation concealment was established using sealed envelopes. The bolus or placebos were prepared by a pharmacist in identical 500 mL bags labelled study infusion. The patients, anesthesiologists, surgeon and all study personnel were blinded to the randomization sequence. The infusion of the assigned treatment was started after induction of anesthesia and after baseline TEE evaluations. A bolus dose of 50 $\mu g \cdot kg^{-1}$ of milrinone was administered over ten minutes followed by an infusion at a rate of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ until skin closure. Patients in the placebo group received an equal volume of normal saline for both bolus and infusions over the same period of time. Treatment of systolic dysfunction at CPB separation with β-agonists and/or nitrates was at the discretion of the anesthesiologist caring for the patient. Unblinding of study treatment was allowed if physicians deemed it necessary for patient care.

Hemodynamic and echocardiographic measurements

Transesophageal echocardiographic measurements of systolic and diastolic function and hemodynamic measurements were performed at the following time points: after the anesthetic induction when the patient was hemodynamically stable (before the administration of milrinone or placebo), after the administration of the bolus dose milrinone or placebo before CPB, and after separation from CPB immediately before sternal closure (after hemodynamic optimization).

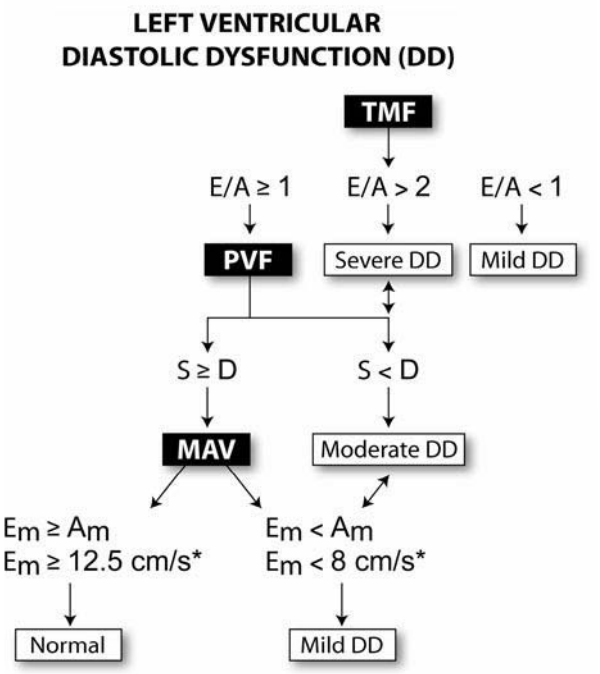

FIGURE 1 Algorithm used in the diagnosis and classification of left ventricular diastolic dysfunction. The diastolic dysfunction is classified using pulsed-wave Doppler of the transmitral (TMF), pulmonary venous flow (PVF) and tissue Doppler examination of mitral annular velocity (MAV). (A = atrial filling A-wave velocity of the TMF; Am = late mitral annular velocity; D = diastolic component of the PVF; E = early filling of the TMF; Em = early mitral annular velocity; S = systolic component of the PVF. Left ventricular diastolic function was graded on a five scale score, ranging from normal to severe diastolic dysfunction. LV diastolic function was graded as: grade 1 (normal) (TMF E/A > 1, PVF S/D > 1, Em/Am > 1), grade 2 (E/A > 1, S/D > 1, Em/Am < 1), grade 3 (E/A < 1, S/D >1, Em/Am <1), grade 4 (E/A > 1, S/D < 1, Em/Am < 1), and grade 5 (E/A > 2, S/D < 1, Em/Am < 1).

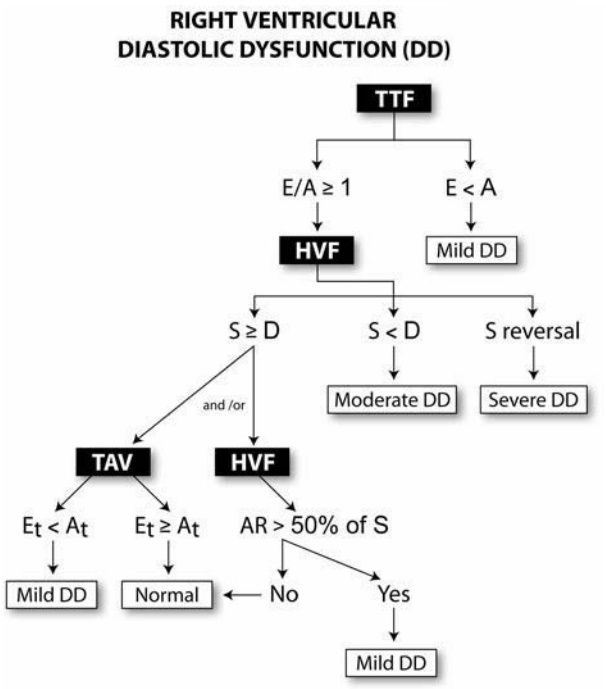

FIGURE 2 Algorithm used in the diagnosis and classification of right ventricular diastolic dysfunction. Diastolic function is classified by pulsed-wave Doppler of the transtricuspid flow (TTF), hepatic venous flow (HVF) and tissue Doppler imaging of the tricuspid annulus or tricuspid annular velocity (TAV). (A = atrial component of the TTF; Ar = reversed atrial flow of the HFV; At = atrial component of the TAV; D = diastolic component of the HVF; E = early filling of the TTF; Et = early component of the TAV; S = systolic component of the HVF).
Right ventricular diastolic dysfunction score was classified as: grade 1 (normal) (TTF E/A > 1, HVF S/D >1, Et/At > 1), grade 2 (E/A < 1, or reversed Ar > 50% of S wave measured on HVF, or Et < At when both E/A and S/D >1), grade 3 (E/A > 1, S/D < 1, Et/At < 1), and grade 4 (S wave reversal on HVF, irrespective of the E/A and S/D ratio).

Following induction of anesthesia and tracheal intubation, a radial artery catheter, a pulmonary artery catheter, and TEE probe (Sonos 5500, Hewlett-Packard, Andover, MA, USA) were placed. Anesthetic drugs consisted of sufentanil (1 $\mu g \cdot kg^{-1}$ *iv* for induction and 1 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ until the end of surgery), midazolam (0.04 $mg \cdot kg^{-1}$ *iv* during induction followed by 0.04 $mg \cdot kg^{-1} \cdot hr^{-1}$), isoflurane (0.5 to 2.0% end-tidal concentration) and pancuronium. Hypotension, defined as mean arterial pressure (MAP) < 60 mmHg or a decrease in MAP > 20% compared to the pre-anesthesia value, before or during CPB, was treated with infusion of phenylephrine.

Transesophageal echocardiographic measurements

A standard TEE examination was performed including assessments of regional and global left and right ventricular function and assessments of mitral, aortic, and tricuspid valve function using colour flow Doppler examination. To assess systolic function, LV end-diastolic area (EDA), end-systolic area (ESA) and LV fractional area change (FAC) were measured from the transgastric midpapillary view. Cavity dimensions were also obtained from the mid-esophageal four-chamber view, the left atrium and right atrium diameter, maximum right ventricular end-diastolic diameter, right ventricular ESA , EDA and FAC were measured using published guidelines.[17]

To assess left and right ventricular diastolic function, pulsed wave (PW) Doppler was used to evaluate transmitral and transtricuspid inflow. To assess transtricuspid flow, we used the mid-esophageal four-chamber view or the mid-esophageal right ventricular inflow-outflow view. We used the incidence with the smallest angle between the Doppler beam and the transtricuspid flow. No correction was made for the angle. Peak early flow velocity (E), peak late diastolic flow velocity (A), and early filling deceleration time were measured for transmitral flow. Pulmonary venous flow and hepatic venous flow were also evaluated using PW Doppler. Peak systolic velocity (S), peak diastolic velocity (D) and peak atrial reversal flow velocity were measured for pulmonary venous and hepatic venous flows. Left ventricular isovolumic relaxation time was measured using PW Doppler with the sampling volume placed at the conjunction of LV inflow and outflow.

Mitral annulus velocities (Sm, Em, Am) were measured at the lateral or anterior mitral annulus (the signal with the best definition and with the higher Em was chosen) by tissue Doppler imaging (TDI). Tricuspid annulus velocities (St, Et, At) were also derived by TDI using a deep transgastric right ventricular long axis view with right side rotation. In this view, the tricuspid annulus is parallel to the Doppler axis.[2,18] Mitral flow propagation velocity (Vp) was also studied with the colour M-mode spectrum. To measure Vp, a four-chamber view was obtained, and the M-mode plane was extended from the apex to the tips of the mitral valve leaflets. A slope was drawn from the mitral valve at the first aliasing velocity during early filling to 4 cm distally into the LV cavity.[19]

All echocardiographic data were recorded on a magnetic optical disk for off-line viewing. The echocardiographic measurements were made off-line by two independent observers blinded to the patient's data. Measurements were taken during a short period of apnea. The average of three consecutive cardiac cycles was used for each measurement. Our inter-observer variability for the assessment of systolic and diastolic function has been published previously.[1,2,4,20,21] The use of the LV diastolic dysfunction and right ventricular diastolic dysfunction criteria were previously validated[2] using Cohen's kappa values.[22] The kappa values were 0.77 and 0.82 for inter-observer agreement for the left and right ventricular evaluations respectively.

The classification of LV diastolic function was based on a modification of the algorithm described by Khouri *et al.*,[19] that we previously validated[2,18] (Figures 1 and 2). There is a hierarchy of measurements for defining diastolic function in this algorithm. Indeed, mitral inflow interrogation is the cornerstone of initial physiologic evaluation, to which pulmonary flow variables add information. Tissue Doppler imaging and flow propagation velocity provide supportive information to better stratify the degree of diastolic dysfunction. When there are discrepancies, more emphasis is given to volume-insensitive modalities such as TDI and flow propagation velocity. Left ventricular diastolic dysfunction was graded on a five-scale score, ranging from normal to severe diastolic dysfunction. Left ventricular diastolic dysfunction score was graded as: grade 1 (normal) (transmitral flow $E/A > 1$, pulmonary venous flow $S/D > 1$, $Em/Am > 1$), grade 2 ($E/A > 1$, $S/D > 1$, $Em/Am < 1$), grade 3 ($E/A < 1$, $S/D > 1$, $Em/Am < 1$), grade 4 ($E/A > 1$, $S/D < 1$, $Em/Am < 1$), and grade 5 ($E/A > 2$, $S/D < 1$, $Em/Am < 1$).

Assessment of right ventricular diastolic function was evaluated using transtricuspid Doppler flow, hepatic venous flow[23] and TDI of the tricuspid annulus (Figure 2). A normal hepatic venous flow was defined as a ratio of systolic to diastolic velocities greater than 1 with the atrial reversal velocity less than half of the maximum systolic wave velocity.[24] Moderate to severe right ventricular diastolic dysfunction was considered present if the systolic waveform was reduced or inverted on the Doppler hepatic venous flow. Right ventricular diastolic dysfunction was graded on a four-scale score. Right ventricular diastolic dysfunction score was classified as: grade 1 (normal) (transtricuspid flow $E/A > 1$, hepatic venous flow $S/D > 1$, $Et/At > 1$), grade 2 ($E/A < 1$, or reversed atrial flow (Ar) > 50% of systolic (S wave) measured on hepatic venous flow, or $Et < At$ when both E/A and $S/D > 1$), grade 3 ($E/A > 1$, $S/D < 1$, $Et/At < 1$), and grade 4 (S wave reversal on hepatic venous flow, irrespective of the E/A and S/D ratio) as described previously.[2]

Hemodynamic measurements consisted of heart rate, blood pressure, central venous pressure (CVP), pulmonary artery pressure (Ppa), pulmonary artery occlusion pressure (Paop), and cardiac index (CI). These measurements were recorded at end-expiration.

Intraoperative observations included the use of different therapies prior, during and after CPB, CPB and aortic cross clamping times and the need and reason to return to CPB. After surgery, observations included the use of different therapies and their durations in the intensive care unit (ICU) (vasodilators, inotropes, vasopressors, intra-aortic balloon pump), the presence of arrhythmia or ischemia, and the duration of ICU and hospital stay. The clinicians in charge of the postoperative management were also blinded to the intraoperative allocation of the study drug.

TABLE I Demographic data

	Milrinone group (n = 25)	*Placebo group (n = 25)*	*P value*
Male [*n* (%)]	19 (76%)	19 (76%)	1.000
Female [*n* (%)]	6 (24%)	6 (24%)	1.000
Age (yr) (mean ± SD)	67 ± 8	70 ± 7	0.158
Weight (kg) (mean ± SD)	80 ± 14	84 ± 16	0.382
Height (cm) (mean ± SD)	167 ± 9	168 ± 9	0.494
Hypertension [*n* (%)]	17 (68%)	22 (88 %)	0.088
Diabetes [*n* (%)]	12 (48%)	10 (40%)	0.569
LV ejection fraction (%) (mean ± SD)	51 ± 15	50 ± 13	0.928
Use of ACE inhibitor [*n* (%)]	10 (40%)	12 (48%)	0.569
Calcium channel blocker [*n* (%)]	15 (60%)	12 (48%)	0.395
Beta-adrenergic blocker [*n* (%)]	19 (76%)	20 (80%)	0.733
Parsonnet score (mean ± SD)	10.2 ± 5.2	10.2 ± 5.8	0.979
CPB time (min) (mean ± SD)	75.3 ± 22.5	70.9 ± 22.4	0.492
Aortic clamping time (min) (mean ± SD)	46.8 ± 16.5	44.8 ± 20.8	0.702
Number of bypasses [median (q1 - q3)]	3 (3 – 4)	3 (3 – 3)	0.279
LVDD score [median (min-max)]	3 (2-4)	3 (3-5)	0.790

LV = left ventricular; ACE = angiotensin converting enzyme; CPB = cardiopulmonary bypass; LVDD = left ventricular diastolic dysfunction score.

Sample size considerations

The primary endpoint of this study was the LV diastolic function score previously described and sample size was based on comparison of the two groups post-bolus. A sample size of 25 patients in each group provided 80% power to detect a difference of 0.5 in LV diastolic function score between groups, assuming a standard deviation of 0.61 and a two-sided 0.05 significance level.

Statistical methods

Data are presented as means ± SD for continuous variables, except for those that were not normally distributed which are presented as median (25^{th} percentile - 75^{th} percentile). Frequencies and percentages are presented for categorical variables. Patient population characteristics and outcomes were compared between the two groups using the Chi-square statistic in case of categorical variables while continuous variables were compared using the Student's *t* test or Mann-Whitney test if distributional assumptions were not met. Because of the distribution of patients among the five-scale score, the generalized estimating equation approach was performed using the multinomial distribution to study the left and right ventricular diastolic function. Repeated measures ANOVA models were used to study the hemodynamic and echocardiographic parameters across time and between groups. Models with time, group and group x time interaction as independent variables were used. Comparisons between groups at a given time point were undertaken only in a presence of a significant group x time interaction. Otherwise, global conclusions were drawn based on the main time and group effects of the model. All analyses were done with SAS version 8.2 (SAS Institute Inc., Cary, NC, USA) and significance was assumed when $P < 0.05$.

Results

Seventy consecutive patients scheduled to undergo CABG were screened. Fifty patients met our criteria for preoperative LV diastolic dysfunction, and all 50 subjects were enrolled and subsequently randomized. TEE probe insertion was unsuccessful for one patient in the milrinone group, and for this patient, the hemodynamic data set only was included in the analysis. All 50 patients completed the study protocol. Demographic data are shown in Table I.

Hemodynamic data

Hemodynamic data are presented in Table II. Significant group x time interactions were observed for CI ($P < 0.0001$), stroke volume ($P = 0.04$), heart rate ($P = 0.03$) and CVP ($P = 0.0247$). There was no significant difference between groups with respect to any of these hemodynamic parameters at baseline (before study drug administration). After bolus administration of the study drug, CI ($P < 0.0001$), stroke volume ($P = 0.02$) and heart rate ($P = 0.01$) were higher and CVP was lower ($P = 0.01$) in the milrinone *vs* placebo group. Patients in the milrinone group required higher doses of phenylephrine to maintain normal systemic arterial pressure during the intraoperative period ($P = 0.03$) (Table VI). Following CPB, CI and stroke volume remained higher in the milrinone group. There was no significant difference between groups for Paop, mean systemic arterial pressure, and mean Ppa during the study.

TABLE II Hemodynamic data

	Time	*Milrinone (mean ± SD)*	*Placebo (mean ± SD)*	*Group x time interaction P-value*	*Group P-value**
HR (beats·min^{-1})	Pre-bolus	55 ± 6	55 ± 12		0.8815
	Post-bolus	67 ± 8	60 ± 12	0.0345	0.0145
	Post-CPB	73 ± 10	70 ± 15		0.3885
MAP (mmHg)	Pre-bolus	89.7 ± 35.6	81.6 ± 11.5		
	Post-bolus	70.3 ± 13.5	78.1 ± 11.4	0.1760	0.4182
	Post-CPB	67.2 ± 9.0	74.3 ± 12.1		
CVP (mmHg)	Pre-bolus	11.4 ± 3.4	12.4 ± 6.1		0.4774
	Post-bolus	9.9 ± 3.5	13.0 ± 5.0	0.0247	0.0130
	Post-CPB	11.0 ± 4.0	13.1 ± 5.1		0.1179
PAOP (mmHg)	Pre-bolus	12.5 ± 3.4	14.1 ± 7.2		
	Post-bolus	12.7 ± 3.5	15.7 ± 5.3	0.2235	0.0555
	Post-CPB	12.8 ± 3.6	13.1 ± 7.0		
MPAP (mmHg)	Pre-bolus	21.4 ± 5.4	23.5 ± 8.9		
	Post-bolus	19.9 ± 4.5	23.2 ± 6.5	0.2777	0.2070
	Post-CPB	20.4 ± 4.3	21.7 ± 9.4		
CI (L·min^{-1}·m^{-2})	Pre-bolus	2.1 ± 0.4	2.0 ± 0.3		0.3069
	Post-bolus	2.8 ± 0.6	2.1 ± 0.5	< 0.0001	< 0.0001
	Post-CPB	3.2 ± 1.0	2.4 ± 0.7		0.0005
SV (mL beats^{-1}·m^{-2})	Pre-bolus	74.3 ± 16.5	73.2 ± 18.0		0.8279
	Post-bolus	78.8 ± 17.1	68.0 ± 15.5	0.0426	0.0214
	Post-CPB	81.3 ± 31.0	68.0 ± 13.6		0.0393

HR = heart rate; MAP = mean arterial pressure; CVP = central venous pressure; PAOP = pulmonary artery occlusion pressure; MPAP = mean pulmonary artery pressure; CI = cardiac index; SV = stroke volume. *Overall group *P*-value in case of a non-significant group x time interaction; Group *P*-value at given time point in case of a significant group x time interaction.

Transesophageal echocardiographic data

Transesophageal echocardiographic data are shown in Tables III and IV. For clarity, only between-groups findings are described for each parameter. There were no statistically significant differences between groups with respect to LV FAC, EDA and ESA, right ventricular FAC and right ventricular maximal end-diastolic diameter during the study period. The right atrial diameter was smaller in the milrinone group ($P = 0.008$) independently of study period compared to the placebo group. The left atrial diameter was higher in the milrinone group compared to placebo specifically after CPB ($P = 0.0319$ for group x time interaction; $P = 0.0175$ for comparison after CPB).

Transmitral and transtricuspid flow Doppler velocities

The transmitral E wave was significantly higher in the milrinone group compared to the placebo group after CPB ($P = 0.048$ for interaction; $P = 0.004$ for comparison after CPB), while no significant difference between groups occurred in the E/A ratio. The transtricuspid E wave did not differ between groups during the study, but a significantly higher transtricuspid flow A wave was observed in the milrinone group after the bolus dose and after CPB ($P = 0.0184$ for interaction; $P = 0.0314$ and $P = 0.0358$ for comparisons after the bolus and after CPB respectively). The transtricuspid E/A ratio did not differ significantly between groups. The groups were similar with respect to deceleration time and isovolumic relaxation times.

Pulmonary venous flow and hepatic venous flow velocities

The S wave of the pulmonary venous flow was significantly higher in the milrinone group compared to placebo after the bolus dose and after CPB ($P = 0.0098$ for group x time interaction; $P = 0.018$ and $P = 0.002$ for comparisons after the bolus and after CPB respectively). The S wave and the S/D ratio of the hepatic venous flow were also higher in the milrinone group after the bolus dose compared to placebo ($P = 0.0061$ and $P = 0.0120$ for group x time interactions respec-

TABLE III Left ventricular echocardiographic data

	Time	*Milrinone (mean ± SD)*	*Placebo (mean ± SD)*	*Group x time interaction P-value*	*Group P-value**
LVFAC	Pre-bolus	0.47 ± 0.14	0.50 ± 0.10		
	Post-bolus	0.54 ± 0.13	0.50 ± 0.13	0.0935	0.7374
	Post-CPB	0.53 ± 0.12	0.51 ± 0.14		
LVESA (cm^2)	Pre-bolus	8.82 ± 3.74	8.35 ± 4.64		
	Post-bolus	7.92 ± 4.41	8.83 ± 4.60	0.0606	0.9364
	Post-CPB	7.95 ± 3.24	8.20 ± 4.05		
LVEDA (cm^2)	Pre-bolus	16.32 ± 4.29	16.12 ± 5.97		
	Post-bolus	16.46 ± 6.14	17.04 ± 5.22	0.6242	0.9283
	Post-CPB	16.57 ± 3.53	16.15 ± 4.43		
LAD (cm)	Pre-bolus	4.45 ± 0.57	4.32 ± 0.62		0.5266
	Post-bolus	4.33 ± 0.74	4.71 ± 0.67	0.0319	0.2596
	Post-CPB	4.81 ± 0.57	4.40 ± 0.51		0.0175
TMF E wave ($cm \cdot sec^{-1}$)	Pre-bolus	64.73 ± 7.04	58.37 ± 4.21		0.1497
	Post-bolus	64.38 ± 5.68	61.12 ± 6.80	0.0480	0.4486
	Post-CPB	77.13 ± 0.96	61.64 ± 5.36		0.0036
TMF A wave ($cm \cdot sec^{-1}$)	Pre-bolus	57.55 ± 6.30	53.58 ± 0.53		
	Post-bolus	65.65 ± 8.36	54.38 ± 1.13	0.1088	0.0066
	Post-CPB	75.23 ± 4.98	57.22 ± 2.65		
TMF E/A wave	Pre-bolus	1.19 ± 0.36	1.52 ± 1.77		
	Post-bolus	1.02 ± 0.28	1.22 ± 0.38	0.9240	0.1028
	Post-CPB	1.05 ± 0.30	1.21 ± 0.56		
PVF S wave ($cm \cdot sec^{-1}$)	Pre-bolus	47.75 ± 0.98	47.41 ± 3.23		0.9222
	Post-bolus	54.93 ± 4.30	44.68 ± 4.10	0.0098	0.0180
	Post-CPB	62.47 ± 4.72	47.78 ± 5.87		0.0021

*Overall group *P*-value in case of a non-significant group x time interaction; Group *P*-value at given time point in case of a significant group x time interaction. LVFAC = left ventricular fractional area change; LVESA = left ventricular end-systolic area; LVEDA = left ventricular end-diastolic area; LAD = left atrial diameter; TMF E wave = transmitral flow early mitral filling-wave velocity; TMF A wave = transmitral flow atrial-wave velocity; TMF E/A wave = transmitral flow early mitral filling/atrial wave velocity; PVF S wave = pulmonary venous flow systolic-wave velocity.

tively; $P = 0.026$ and $P = 0.0022$ for comparisons after the bolus respectively). There was no significant difference in the diastolic component of the pulmonary venous and hepatic venous flows between the study arms during the study period.

Tissue Doppler imaging of the mitral and tricuspid annulus

The Am wave of the mitral annulus was higher in the milrinone group after CPB compared with placebo ($P = 0.0220$ for group x time interaction; $P = 0.0015$ for comparison after CPB). The At wave of the tricuspid annulus was also higher in the milrinone group after the bolus dose and after CPB ($P = 0.0069$ for group x time interaction; $P = 0.04$ and $P = 0.01$ for comparisons after the bolus and after CPB respectively). No significant changes in Em, Et, and Et/At ratio were observed during the study between groups while the Em/Am ratio was significantly lower post-CPB in the milrinone group. The Sm wave of the mitral annulus did not differ significantly between study arms. However, the St wave of the tricuspid annulus was higher in the milrinone group after the bolus dose and after CPB ($P = 0.0370$ for group x time interaction; $P = 0.004$ and $P = 0.018$ for comparisons after the bolus and after CPB respectively).

Mitral flow propagation velocity

No significant difference in Vp was observed between groups during the study.

TABLE III Left ventricular echocardiographic data (*continued*)

	Time	*Milrinone (mean ± SD)*	*Placebo (mean ± SD)*	*Group x time interaction P-value*	*Group P-value**
PVF D wave ($cm \cdot sec^{-1}$)	Pre-bolus	34.96 ± 1.12	33.63 ± 0.58		
	Post-bolus	35.01 ± 0.19	30.13 ± 1.83	0.0847	0.0532
	Post-CPB	50.76 ± 1.68	40.24 ± 4.08		
PVF S/D	Pre-bolus	1.45 ± 0.39	1.49 ± 0.44		
	Post-bolus	1.64 ± 0.47	1.65 ± 0.64	0.8961	0.9250
	Post-CPB	1.32 ± 0.35	1.28 ± 0.50		
Em ($cm \cdot sec^{-1}$)	Pre-bolus	7.00 ± 1.45	7.01 ± 1.53		
	Post-bolus	7.01 ± 1.69	7.12 ± 1.68	0.9650	0.7733
	Post-CPB	7.54 ± 2.30	7.74 ± 2.75		
Am ($cm \cdot sec^{-1}$)	Pre-bolus	8.65 ± 2.62	8.90 ± 1.56		0.6918
	Post-bolus	10.00 ± 2.26	9.28 ± 2.65	0.0220	0.3154
	Post-CPB	10.49 ± 2.67	8.35 ± 1.84		0.0015
Em/Am	Pre-bolus	0.87 ± 0.33	0.81 ± 0.24		0.4639
	Post-bolus	0.73 ± 0.21	0.83 ± 0.33	0.0222	0.1833
	Post-CPB	0.74 ± 0.21	1.37 ± 1.88		0.0220
Sm ($cm \cdot sec^{-1}$)	Pre-bolus	7.00 ± 1.67	6.92 ± 1.58		
	Post-bolus	8.39 ± 2.77	7.51 ± 1.60	0.1133	0.1340
	Post-CPB	8.30 ± 2.40	7.23 ± 1.88		
Colour M mode ($cm \cdot sec^{-1}$)	Pre-bolus	45.64 ± 2.30	51.81 ± 7.35		
	Post-bolus	42.07 ± 2.42	42.35 ± 4.56	0.1675	0.5994
	Post-CPB	57.16 ± 5.39	41.98 ± 4.23		

*****Overall group *P*-value in case of a non-significant group x time interaction; Group *P*-value at given time point in case of a significant group x time interaction. PVF D wave= pulmonary venous flow D wave velocity; PVF S/D = pulmonary venous flow systolic/diastolic wave velocities; Em = early mitral filling E-wave velocity; Am = late mitral annular velocity; Sm = systolic mitral annular velocity.

Left and right ventricular diastolic function

Left and right ventricular diastolic dysfunction scores are shown in Table V. The LV diastolic dysfunction score (primary outcome variable) did not differ significantly between groups during the study (non-significant group x time interaction; $P = 0.199$ for main group effect and $P = 0.283$ for main time effect). The right ventricular diastolic function score was slightly higher in the placebo group at baseline ($P = 0.041$ for main group effect). No difference for right ventricular diastolic function between groups was observed in response to the bolus dose and after CPB. The group-time interaction was not assessed because patients were not evenly distributed among the five-scale score and the model including time, group and group-time did not converge.

Postoperative course and patient outcomes

Outcome variables are shown in Table VI. Nineteen patients in the milrinone group and 17 patients in the placebo group required norepinephrine in the ICU. Five patients in each group required two or more inotropic agents while in ICU. There were no differences between groups with respect to norepinephrine requirements during the intraoperative period and ICU, duration of postoperative ventilation, lengths of stay in the ICU, and hospital lengths of stay. Two patients in the milrinone group died secondary to multi-organ failure, 12 and 34 days after the surgical procedure. There were no deaths in the placebo group, and no patient experienced myocardial infarction, postoperative ventricular fibrillation or cardiogenic shock. Two patients in the milrinone group and one in the placebo group developed acute renal failure.

Discussion

Our study evaluated the effect of prophylactic milrinone (given before CPB) on biventricular diastolic function in patients with LV diastolic dysfunction

TABLE IV Right ventricular echocardiographic data

	Time	*Milrinone (mean ± SD)*	*Placebo (mean ± SD)*	*Group x time interaction P-value*	*Group P-value**
RVFAC	Pre-bolus	0.42 ± 0.15	0.43 ± 0.12		
	Post-bolus	0.49 ± 0.13	0.45 ± 0.11	0.2102	0.1298
	Post-CPB	0.53 ± 0.11	0.45 ± 0.12		
RVD (cm)	Pre-bolus	3.50 ± 0.59	3.73 ± 0.72		
	Post-bolus	3.54 ± 0.66	3.82 ± 0.55	0.1842	0.0825
	Post-CPB	3.68 ± 0.43	3.83 ± 0.52		
RAD (cm)	Pre-bolus	4.64 ± 0.83	4.79 ± 0.82		
	Post-bolus	4.45 ± 0.77	5.01 ± 1.01	0.0860	0.0086
	Post-CPB	4.30 ± 0.59	5.17 ± 0.87		
TTF E wave ($cm \cdot sec^{-1}$)	Pre-bolus	35.88 ± 6.44	35.76 ± 12.31		
	Post-bolus	43.34 ± 12.78	35.61 ± 9.36	0.2590	0.2077
	Post-CPB	37.41 ± 8.68	35.64 ± 8.89		
TTF A wave ($cm \cdot sec^{-1}$)	Pre-bolus	28.34 ± 9.89	31.09 ± 14.33		0.6444
	Post-bolus	38.56 ±12.24	30.98 ± 10.02	0.0184	0.0314
	Post-CPB	42.24 ± 16.33	32.64 ± 9.17		0.0358
TTF E/A	Pre-bolus	1.42 ± 0.60	1.21 ± 0.30		
	Post-bolus	1.17 ± 0.29	1.19 ± 0.32	0.0629	0.7570
	Post-CPB	0.92 ± 0.37	1.22 ± 0.57		
HVF S wave ($cm \cdot sec^{-1}$)	Pre-bolus	21.86 ± 7.98	22.64 ± 9.21		0.8432
	Post-bolus	33.75 ± 16.29	20.06 ± 7.89	0.0061	0.0026
	Post-CPB	19.40 ± 23.00	14.53 ± 17.68		0.6101
HVF D wave ($cm \cdot sec^{-1}$)	Pre-bolus	13.55 ± 5.74	16.68 ± 7.78		
	Post-bolus	20.01 ± 10.62	19.19 ± 10.80	0.2946	0.8615
	Post-CPB	25.14 ± 9.38	22.51 ± 12.42		

*****Overall group *P*-value in case of a non-significant group x time interaction; Group *P*-value at given time point in case of a significant group x time interaction. RVFAC = right ventricular fractional area change; RVD = right ventricular dysfunction; RAD = right atrial diameter; TTF E wave = transtricuspid flow early mitral filling E-wave velocity; TTF A wave = transtricuspid flow atrial filling A-wave velocity; HVF S wave = hepatic venous flow systolic S-wave velocity; HVF D wave = hepatic venous flow diastolic D-wave velocity.

undergoing coronary revascularization. While milrinone increased cardiac index and stroke volume, using specific criteria for evaluation of biventricular diastolic function[2,19,23] milrinone administration was not associated with an improvement in LV diastolic dysfunction and right ventricular diastolic dysfunction scores. Patients receiving milrinone required a higher dose of phenylephrine intraoperatively to maintain normal systemic arterial pressure. These patients also tended to require higher doses of norepinephrine during the intraoperative and postoperative periods compared to the placebo group.

Despite milrinone's improvement of global hemodynamic indices, we did not observe an increase in LV FAC in contrast to others.[9,15] The increase in CI may be partly explained by a significant increase in heart rate. Even if stroke volume was significantly increased in the milrinone group, the LV FAC was unchanged. Because the transgastric view at the mid-papillary level was the only TEE image obtained to estimate LV ejection fraction, improvements in regional wall motion abnormalities may have been missed in apical and basal segments in some patients. This index of global cardiac function is also load-dependent, and changes in loading conditions may have contributed to an observed lack of response to the primary intervention.

Other echocardiographic observations in our study suggest increased ventricular systolic function and atrial contraction. There were increases in S velocity from pulmonary venous and hepatic venous flows in response to milrinone, which may be partly explained

TABLE IV Right ventricular echocardiographic data (*continued*)

	Time	*Milrinone (mean ± SD)*	*Placebo (mean ± SD)*	*Group x time interaction P-value*	*Group P-value**
HVF A wave ($cm \cdot sec^{-1}$)	Pre-bolus	11.22 ± 6.35	15.22 ± 9.75		
	Post-bolus	19.21 ± 9.49	19.66 ± 5.26	0.3932	0.3102
	Post-CPB	15.72 ± 6.52	20.25 ± 2.22		
HVF S/D	Pre-bolus	1.72 ± 0.56	1.42 ± 0.36		0.0369
	Post-bolus	1.81 ± 0.66	1.20 ± 0.48	0.0120	0.0022
	Post-CPB	0.74 ± 0.77	0.84 ± 0.69		0.6503
Et ($cm \cdot sec^{-1}$)	Pre-bolus	6.42 ± 1.83	5.16 ± 1.01		
	Post-bolus	6.13 ± 1.23	5.91 ± 1.99	0.0965	0.0226
	Post-CPB	6.49 ± 2.67	5.01 ± 1.14		
At ($cm \cdot sec^{-1}$)	Pre-bolus	8.64 ± 1.73	9.06 ± 2.37		0.6022
	Post-bolus	10.03 ± 3.63	7.94 ± 2.67	0.0069	0.0424
	Post-CPB	10.34 ± 3.63	7.48 ± 2.61		0.0109
Et/At	Pre-bolus	0.76 ± 0.27	0.59 ± 0.13		0.0259
	Post-bolus	0.66 ± 0.20	0.78 ± 0.26	0.0065	0.1130
	Post-CPB	0.67 ± 2.10	0.73 ± 0.20		0.5080
St ($cm \cdot sec^{-1}$)	Pre-bolus	7.20 ± 2.16	7.06 ± 1.80		0.7151
	Post-bolus	9.97 ± 3.82	7.03 ± 2.21	0.0370	0.0040
	Post-CPB	8.54 ± 2.61	6.62 ± 1.92		0.0180

*Overall group p-value in case of a non-significant group x time interaction; Group *P*-value at given time point in case of a significant group x time interaction. HVF A wave = hepatic venous flow atrial filling A-wave velocity; HVF S/D = hepatic venous flow systolic/diastolic wave velocities; Et = early filling tricuspid annular velocity; At = atrial filling tricuspid annular velocity. St = systolic tricuspid annular velocity.

by an increase in ventricular contraction.[25] The At and St waves of the tricuspid annulus along with an increase in transtricuspid A wave suggest improvements in right atrial and systolic ventricular function in the milrinone group. A higher Am velocity of the mitral annulus was also observed after CPB in the milrinone group and could reflect increased left atrial contractile function.

The importance of LV diastolic dysfunction in cardiac surgery has been recognized.[1–3,26] Preoperative LV diastolic dysfunction has been shown to be a strong predictor of inotropic support following CPB.[1] Left ventricular diastolic dysfunction is also associated with a longer hospital stay and was also an independent predictor of cardiac events one year following surgery.[3] We have also observed that more severe forms of LV diastolic dysfunction before surgery are associated with difficult separation from CPB,[2] and difficult separation from CPB is an independent predictor of postoperative hemodynamic complications.[27] In this study, however, milrinone administration was not associated with an improvement in either LV or right ventricular diastolic dysfunction scores. In contrast, a favourable effect of milrinone on LV diastolic dysfunction has been documented in patients with congestive heart failure.[14] An increase in the peak negative dP/dt, a decrease in Tau, and an increase in LV peak filling rate were observed after milrinone administration, which suggested improved LV diastolic relaxation and chamber distensibility. However, three studies have evaluated the effect of milrinone on LV diastolic function in cardiac surgical patients and found contradictory results. In one of these studies, Lobato *et al.*[10] compared the effect of epinephrine infusion to a bolus and infusion of milrinone 50 $\mu g \cdot kg^{-1}$ given after the weaning of CPB on LV diastolic dysfunction in 20 patients undergoing CABG. Left ventricular compliance was assessed by observing changes in LV EDA in the short-axis view with TEE, while maintaining a constant left atrial pressure. Left ventricular compliance was reduced after CPB, and the administration of milrinone was associated with a partial return to pre-CPB values. In another study, Maslow *et al.*[15] evaluated the effects of milrinone and epinephrine given immediately before weaning from CPB on hemodynamics in patients undergoing aortic valve replacement for aortic stenosis. Criteria used to define patterns of diastolic dysfunction were similar

TABLE V Left and right ventricular diastolic function

Time	*Score*	*Milrinone (n (%))*	*Placebo (n (%))*	*Group x time interaction P value*	*Group P value*	*Time P value*
LVDD						
Pre-bolus	1	0 (0)	0 (0)			
	2	14 (58)	6 (25)			
	3	7 (29)	15 (63)			
	4	3 (13)	2 (8)			
	5	0 (0)	1 (4)			
Post-bolus	1	0 (0)	0 (0)			
	2	7 (33)	11 (46)			
	3	14 (67)	9 (37)	0.2029	0.1989*	0.2834*
	4	0 (0)	4 (17)			
	5	0 (0)	0 (0)			
Post-CPB	1	0 (0)	2 (9.5)			
	2	8 (33)	4 (19)			
	3	14 (58)	9 (43)			
	4	2 (8)	4 (19)			
	5	0 (0)	2 (9.5)			
RVDD						
Pre-bolus	1	1 (5)	0 (0)			
	2	18 (95)	17 (90)			
	3	0 (0)	2 (10)	-	0.0407**	-
	4	0 (0)	0 (0)			
	5	0 (0)	0 (0)			
Post-bolus	1	0 (0)	0 (0)			
	2	19 (91)	15 (75)			
	3	2 (9)	5 (25)	-	0.1827**	-
	4	0 (0)	0 (0)			
	5	0 (0)	0 (0)			
Post-CPB	1	0 (0)	0 (0)			
	2	6 (32)	10 (43.5)			
	3	10 (52)	10 (43.5)	-	0.4664**	-
	4	3 (16)	3 (13)			
	5	0 (0)	0 (0)			

*Overall *P* value in case of a non significant group x time interaction; **Generalized estimating equation (GEE) model including group as independent variable was performed at each time point because patients were not evenly distributed among the five-scale score and the model including time, group and group*time did not converge. LVDD score = left ventricular diastolic dysfunction score; RVDD score = right ventricular diastolic dysfunction score. CPB = cardiopulmonary bypass.

to those used in our study. There were no changes in pulmonary venous flow or transmitral flow, and study groups had similar numbers of patients with normal and abnormal patterns of diastolic function before and after CPB, which suggested that milrinone had no immediate effects on diastolic function compared with placebo. Finally Lobato *et al.*[16] in a similar study of patients undergoing CABG compared epinephrine and milrinone using the newer echocardiographic modalities for the evaluation of diastolic function. These investigators found that neither epinephrine nor milrinone exhibited favourable lusitropic effect.

Our results evaluating the effect of milrinone on diastolic function differ from those of Monrad *et al.*[14] and Lobato *et al.*[10] but are in agreement with the study of Maslow *et al.*[15] and the more recent study of Lobato.[16] Many factors can explain the different results found in these studies. First, patients with advanced congestive heart failure were studied by Monrad *et al.*[14] patients undergoing CABG but without documented LV diastolic dysfunction were included in the study of Lobato *et al.*[10] and patients with aortic stenosis were selected by Maslow *et al.*[15] The effect of milrinone on diastolic function may differ in these populations. Our study included patients with ischemic heart disease and varying degrees of LV diastolic dysfunction. Unlike previous studies, milrinone was administered in our study before CPB to avoid the potentially confounding effects of CPB and CABG on diastolic function and study more

TABLE VI Outcome variables

	Milrinone group (n = 25)	*Placebo group (n = 25)*	*P-value*
Atrial fibrillation duration (hr) [median (q1 - q3)]	0 (0 - 0)	0 (0 - 1)	0.389
Norepinephrine in ICU (hr) [median (q1 - q3)]	2 (0.3 - 5)	1 (0- 6)	0.531
Norepinephrine in ICU (doses in µg) [median (q1 - q3)]	12.8 (3.2 - 400)	38.4 (0 - 320)	0.907
Duration of ventilation (hr) [median (q1 - q3)]	12 (8 - 14)	9 (7 - 14)	0.312
ICU stay (days) [median (q1 - q3)]	2 (1 - 2)	1.8 (1 - 2)	0.844
Hospital length of stay (days) [median (q1 - q3)]	5 (4 - 7)	5 (4 - 6)	0.573
Norepinephrine in OR (doses in µg) (mean ± SD)	400 ± 448	240 ± 256	0.124
Phenylephrine in OR (doses in mg) (mean ± SD)	10.6 ± 7	4.8 ± 4.2	0.027
Nitroglycerin in OR (doses in mg) (mean ± SD)	2.5 ± 2.6	4.0 ± 3.4	0.100
Acute renal failure [*n* (%)]	2 (8%)	1 (4%)	0.552
Norepinephrine in the ICU [*n* (%)]	19 (76)	17 (68)	0.529
>= 2 inotropic agents in the ICU [*n* (%)]	5 (20)	5 (20)	1.000

ICU = intensive care unit; OR = operating room.

specifically, the effect of milrinone on diastolic filling patterns.

There are several limitations of this study. The gold standards for evaluating diastolic dysfunction are the time constant of relaxation (Tau) and pressure-volume curves obtained by direct invasive measurements to assess chamber compliance. However, these measures are invasive and are not feasible in usual practice. We used Doppler assessment of mitral inflow and pulmonary flow variables to assess diastolic function. Tissue Doppler imaging and flow propagation velocity, which are relatively volume-insensitive modalities, provided supportive information to better stratify the degree of diastolic dysfunction.[19] Changes in mitral flow velocity have been noted with changes in loading conditions, differing heart rates, and the LV contractile state.[25] Even if patients of the milrinone group received higher doses of phenylephrine, we obtained similar loading conditions between the two groups (no difference in Paop, mean systemic arterial pressure and mean pulmonary arterial pressure), and the heart rate was only slightly greater in the milrinone group (60 ± 12 in the placebo group *vs* 67 ± 8 beats·min^{-1} in the milrinone group) which should not have greatly influenced the transmitral flow. While the effect of the increased cardiac output on pulmonary venous flow is known (the S wave increase with an increase in cardiac output),[25] the effect of cardiac output on mitral inflow is not well documented. It is possible that a change in contractility or heart rate may have influenced the TMF. The effect of improved contractility in the milrinone group should not be ignored, but should rather have resulted in increased mitral inflow velocities, which was not observed. In addition, in agreement with Khouri *et al.*[19] we also used pulmonary venous flow pattern, and other modalities, which are relatively load independent, such as TDI and flow propagation velocity. Despite this fact, we cannot totally exclude the effect of the increase in cardiac output, heart rate and phenylephrine infusion on the observed diastolic filling pattern in our patients. Using load-independent modalities[19] milrinone was not associated with an improvement in diastolic function.

Diastolic dysfunction can be related to many predisposing factors. In our study, we screened consecutive patients for diastolic dysfunction and many elderly or hypertensive patients were studied. Female gender, diabetes, and LV hypertrophy are also predisposing factors and they were equally distributed between groups. Patients with valvular disease were excluded from this study. Even if diastolic function is abnormal in mitral valve disease and aortic stenosis, correct interpretation of diastolic dysfunction is difficult in patients with such conditions. The relevance of our study is underscored by the fact that in the studies of Bernard *et al.*[1] and Denault *et al.*[2] diastolic dysfunction was associated with hemodynamic instability. Criteria for right ventricular diastolic dysfunction have been previously described[23] but are not yet as widely accepted as those used for LV diastolic dysfunction. Even with the best effort to minimize the ultrasound beam to tricuspid flow angle to less than 20, we cannot totally eliminate the effect of the angle on transtricupid A and E wave velocity measurements. Nevertheless, we have previously shown that preoperative right ventricular diastolic dysfunction was associated with an increased need for vasoactive drug support after surgery.[2,5] The effect of milrinone on the CVP may have contributed to some of observed changes in right ventricular filling parameters. We observed in the milrinone group that the At and St waves of the tricuspid annulus and an increase in transtricuspid A wave, which suggest

improvements in right atrial and systolic ventricular function in the milrinone group. This is also consistent with an increase in CI and an increase in venous return. Finally, this study was not powered to detect a difference in clinical outcomes between groups. However, the OPTIME trial, the largest published study comparing intravenous milrinone to placebo in patients with heart failure, did not show any difference in outcomes but, similar to our study, an increase in the use of vasoactive agents for hypotension was observed.[28]

In conclusion, considering the above limitations, we found that using newer Doppler modalities which are relatively load-independent, intraoperative administration of milrinone in patients undergoing CABG is associated with improved LV systolic function, but this inotrope does not improve biventricular diastolic function.

APPENDIX Abbreviations

A = atrial filling A-wave velocity
Am = late mitral annular velocity
Ar = reversed atrial flow
At = atrial filling tricuspid annular velocity
CABG = coronary artery bypass grafting
CPB = cardiopulmonary bypass
D = diastolic D-wave velocity
DT = E-wave deceleration time
E = early mitral filling E-wave velocity
Em = early mitral annular velocity
Et = early filling tricuspid annular velocity
EDA = end-diastolic area
ESA = end-systolic area
FAC = fractional area change
HVF = hepatic venous flow
IVRT = isovolumic relaxation time
LAD = left atrial diameter
LVDD = left ventricular diastolic dysfunction
LVEF = left ventricular ejection fraction
MAV = mitral annular velocity
PVF = pulmonary venous flow
PW = pulsed wave
RAD = right atrial diameter
RVDD = right ventricular diastolic dysfunction
S = systolic S-wave velocity
Sm = systolic mitral annular velocity
St = systolic tricuspid annular velocity
TAV = tricuspid annular velocity
TDI = tissue Doppler imaging
TMF = transmitral flow
TTF =transtricuspid flow
Vp = colour M mode propagation velocity

References

1 *Bernard F, Denault A, Babin D, et al.* Diastolic dysfunction is predictive of difficult weaning from cardiopulmonary bypass. Anesth Analg 2001; 92: 291–8.

2 *Denault AY, Couture P, Buithieu J, et al.* Left and right ventricular diastolic dysfunction as predictors of difficult separation from cardiopulmonary bypass. Can J Anesth 2006; 53: 1020–9.

3 *Liu J, Tanaka N, Murata K, et al.* Prognostic value of pseudonormal and restrictive filling patterns on left ventricular remodeling and cardiac events after coronary artery bypass grafting. Am J Cardiol 2003; 91: 550–4.

4 *Costachescu T, Denault A, Guimond JG, et al.* The hemodynamically unstable patient in the intensive care unit: hemodynamic vs. transesophageal echocardiographic monitoring. Crit Care Med 2002; 30: 1214–23.

5 *Carricart M, Denault AY, Couture P, et al.* Incidence and significance of abnormal hepatic venous Doppler flow velocities before cardiac surgery. J Cardiothorac Vasc Anesth 2005; 19: 751–8.

6 *Hardy JF, Searle N, Roy M, Perrault J.* Amrinone, in combination with norepinephrine, is an effective first-line drug for difficult separation from cardiopulmonary bypass. Can J Anaesth 1993; 40: 495–501.

7 *Sherry KM, Locke TJ.* Use of milrinone in cardiac surgical patients. Cardiovasc Drugs Ther 1993; 7: 671–5.

8 *Kikura M, Levy JH, Bailey JM, et al.* A bolus dose of 1.5 mg/kg amrinone effectively improves low cardiac output state following separation from cardiopulmonary bypass in cardiac surgical patients. Acta Anaesthesiol Scand 1998; 42: 825–33.

9 *Lobato EB, Florete O Jr, Bingham HL.* A single dose of milrinone facilitates separation from cardiopulmonary bypass in patients with pre-existing left ventricular dysfunction. Br J Anaesth 1998; 81: 782–4.

10 *Lobato EB, Gravenstein N, Martin TD.* Milrinone, not epinephrine, improves left ventricular compliance after cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2000; 14: 374–7.

11 *Solina A, Papp D, Ginsberg S, et al.* A comparison of inhaled nitric oxide and milrinone for the treatment of pulmonary hypertension in adult cardiac surgery patients. J Cardiothorac Vasc Anesth 2000; 14: 12–7.

12 *Yamada T, Takeda J, Katori N, Tsuzaki K, Ochiai R.* Hemodynamic effects of milrinone during weaning from cardiopulmonary bypass: comparison of patients with a low and high prebypass cardiac index. J Cardiothorac Vasc Anesth 2000; 14: 367–73.

13 *Feneck RO, Sherry KM, Withington PS, Oduro-Dominah A; European Milrinone Multicenter Trials Group.* Comparison of the hemodynamic effects of

milrinone with dobutamine in patients after cardiac surgery. J Cardiothorac Vasc Anesth 2001; 15: 306–15.

14 *Monrad ES, McKay RG, Baim DS, et al.* Improvement in indexes of diastolic performance in patients with congestive heart failure treated with milrinone. Circulation 1984; 70: 1030–7.

15 *Maslow AD, Regan MM, Schwartz C, Bert A, Singh A.* Inotropes improve right heart function in patients undergoing aortic valve replacement for aortic stenosis. Anesth Analg 2004; 98: 891–902.

16 *Lobato EB, Willert JL, Looke TD, Thomas J, Urdaneta F.* Effects of milrinone versus epinephrine on left ventricular relaxation after cardiopulmonary bypass following myocardial revascularization: assessment by color m-mode and tissue Doppler. J Cardiothorac Vasc Anesth 2005; 19: 334–9.

17 *Lang RM, Bierig M, Devereux RB, et al; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography.* Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005; 18: 1440–63.

18 *Denault AY, Couture P, Buithieu J, Tardif JC.* Transesophageal Echocardiography Multimedia Manual: A Perioperative Transdisciplinary Approach. Marcel Dekker; 2005.

19 *Khouri SJ, Maly GT, Suh DD, Walsh TE.* A practical approach to the echocardiographic evaluation of diastolic function. J Am Soc Echocardiogr 2004; 17: 290–7.

20 *Couture P, Denault AY, Carignan S, Boudreault D, Babin D, Ruel M.* Intraoperative detection of segmental wall motion abnormalities with transesophageal echocardiography. Can J Anesth 1999; 46: 827–31.

21 *Hache M, Denault A, Belisle S, et al.* Inhaled epoprostenol (prostacyclin) and pulmonary hypertension before cardiac surgery. J Thorac Cardiovasc Surg 2003; 125: 642–9.

22 *Fleiss JL.* Statistical Methods for Rates and Proportions, 2nd ed. New York: Wiley Interscience; 1981.

23 *Klein AL, Hatle LK, Burstow DJ, et al.* Comprehensive Doppler assessment of right ventricular diastolic function in cardiac amyloidosis. J Am Coll Cardiol 1990; 15: 99–108.

24 *Appleton CP, Hatle LK, Popp RL.* Superior vena cava and hepatic vein Doppler echocardiography in healthy adults. J Am Coll Cardiol 1987; 10: 1032–9.

25 *Nishimura RA, Abel MD, Hatle LK, Tajik AJ.* Relation of pulmonary vein to mitral flow velocities by transesophageal Doppler echocardiography. Effect of different loading conditions. Circulation 1990; 81: 1488–97.

26 *Vaskelyte J, Stoskute N, Kinduris S, Ereminiene E.* Coronary artery bypass grafting in patients with severe left ventricular dysfunction: predictive significance of left ventricular diastolic filling pattern. Eur J Echocardiogr 2001; 2: 62–7.

27 *Robitaille A, Denault AY, Couture P, et al.* Importance of relative pulmonary hypertension in cardiac surgery: the mean systemic-to-pulmonary artery pressure ratio. J Cardiothorac Vasc Anesth 2006; 20: 331–9.

28 *Cuffe MS, Califf RM, Adams KF Jr, et al; Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) Investigators.* Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. JAMA 2002; 87: 1541–7.