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Inhaled Milrinone: A New Alternative in Cardiac Surgery?

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The administration of milrinone through inhalation has been studied in only a few animal and human studies. Compared to the intravenous administration, inhaled milrinone has been shown to reduce pulmonary artery pressure without systemic hypotension. Therefore, this approach could represent an alternative to nitric oxide. This current state of knowledge of intravenous and inhaled milrinone is presented and summarized.

Keywords: milrinone; pulmonary artery pressure; nitric oxide; heart failure

Studies on Intravenous Milrinone in Cardiac Surgery

Milrinone is a commonly used agent in cardiology and in cardiac surgery for the treatment of left and right ventricular failure. Milrinone is a phosphodiesterase inhibitor (PDI) that decreases the rate of cyclic adenosine monophosphate (cAMP) degradation. The ensuing increase in cAMP leads to enhanced calcium influx into the cell, a rise in cell calcium concentration, and increased contractility. These drugs also cause systemic arterial and venous dilation via inhibition of peripheral phosphodiesterase from a mechanism that is independent of $ß_1$-adrenergic receptor stimulation.[1,2] It has also been shown that milrinone and other PDIs improve the response to β-adrenergic drugs and potentiate the actions of dobutamine.[3]

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As of 2006, a total of 77 randomized controlled trials on intravenous milrinone have been published in the literature. The studies evaluating or comparing the use of milrinone in cardiac surgery are summarized in Table 1. The majority of these studies were performed on patients undergoing coronary revascularization. In adult cardiac surgery, the largest number of patients studied was 140[4] and in neonatal and pediatric cardiac congenital surgery, the largest number of patients studied was 238.[5] Use of a bolus, dosage, timing in relation to cardiopulmonary bypass (CPB) varied greatly between studies. The primary endpoint in most studies has been physiological outcomes. Clinical outcomes, such as weaning from bypass or hospital stay has been considered only in a few studies. The results of these studies are briefly outlined.

Physiological Effects of Milrinone From Randomized Controlled Trials

Hemodynamic Effects

Most studies have shown that milrinone increases cardiac index [5-11] most likely through an increase in cAMP.[12,13] However, the use of intravenous milrinone has also been associated with an increased incidence of hypotension requiring vasoactive support.[7,10,14,15] Hypotension can be mediated through several mechanisms such as systemic vasodilatation and possibly left and right ventricular outflow tract obstruction.[16] In the large randomized trial in acutely decompensated chronic heart failure, Outcomes

Table 1. Clinical Studies on the Use of Milrinone in Cardiac Surgery

Author	Reference	n	Population	Dosage	Timing	Result
1-De Hert et al 1995	73	20	Coronary revascularization	Milrinone 20 µg/kg Milrinone 40 µg/kg (n = 10 per group)	After CPB	Similar CI between group The 40 µg/kg group had higher vasoactiveNE requirement
2-Kikura et al 1995	34	27	Cardiac surgical patients	Milrinone 50-75 µg/kg/min + perfusion 0.5-0.75 µg/kg/min (n = 17) Placebo (n = 10)	During CPB	No change in platelet number or function
3-Doolan et al. 1997	37	30	LVEF 35% PCWP 20 mmHg pre-bypass	Milrinone bolus 50 µg/kg + perfusion 0.5 µg/kg/min Placebo (n = 15 per group)	15 minutes before end of CPB	All patients with milrinone weaned from bypass vs 5/15 placebo
4-Kikura et al. 1997	6	37	Post-CPB patients on catecholamines	Placebo (n = 10) Milrione bolus 50 µg/kg (n = 8) Bolus 50 µg/kg and perfusion of 0.5 µg/kg/min (n = 10) Bolus 75 µg/kg and perfusion 0.75 µg/kg/min (n = 9)	After CPB	Higher CI and velocity of shortening measured by TEE in all 3 milrinone groups
5-Rathmell et al 1998	17	44	Elective cardiac surgery	Amrinone 0.75 mg/kg Milrinone 25 µg/kg (n = 22 per group)	After CPB	Amrinone and milrinone produced similar hemodynamic effects.
6-Lobato et al 1998	7	21	Coronary revascularization	Milrinone bolus 50 µg/kg (n = 11) Placebo (n = 10)	After CPB	Milrinone increase CI, no change in PAP. Less dobutamine required
7-Mollhoff et al 19989	31	22	Coronary revascularization	Milrinone 30 µg/kg with 0.5 µg/kg/min perfusion Placebo (n = 11 per group)	Before CPB	Milrinone did not prevent GI acidosis but reduced IL-6
8-McNicol et al 1999	32	24	Coronary revascularization	Milrinone during CPB Dopamine during CPB Placebo (n = 8 per group)	During CPB	Neither drug prevented splanchnic and systemic endotoxin levels
9-Hamada et al 1999	74	30	Open heart surgery	Milrinone 50 µg/kg after declamping Amrinone 1 mg/kg Placebo (n = 10 per group)	During CPB after declamping	Milrinone and amrinone increase cardiac index and reduce SVR. No change in PAP
10-Hayashida et al 1999	28	24	Coronary revascularization	Milrinone 0.5 µg/kg/min Placebo (n = 12 per group)	After induction of anesthesia X 24 hours	LIMA blood flow greater with milrinone

11-Hayashida et al 1999	12	24	Coronary revascularization	Milrinone 0.5 μg/kg/min Placebo (n = 12 per group)	After induction of anesthesia X 24 hours	Milrinone increase c-AMP and reduces IL-1b and IL-6 after CPB
12-Yamada et al. 2000	14	48	Patients with a low pre-CPB CI <2.5 L/min/m2) and in patients with a high pre-CPB CI (> or =2.5 L/min/m^2)	(1) low pre-CPB CI/placebo, (2) low pre-CPB CI/milrinone, (3) high pre-CPB CI/placebo (4) high pre-CPB CI/milrinone Dose: milrinone 20 μg/kg and perfusion 0.2 μg/kg/min (n = 12 per group)	15 minutes before end of CPB	Infusion of epinephrine in 5 of the 12 patients for hemodynamic support in placebo vs norepinephrine in 6 of 12 patients in the low pre-CPB CI groups receiving milrinone
13-Lobato et al 2000	29	20	Coronary revascularization	Milrinone 50 μg/kg Epinephrine 0.03 μg/kg/min (n = 10 per group)	After separation from CPB	LIMA blood flow greater with milrinone
14-Lobato et al 2000	23	20	Coronary revascularization	Milrinone 50 μg/kg Epinephrine 0.03 μg/kg/min (n = 10 per group)	After separation from CPB	Milrinone maintained left ventricular compliance (measured as LVEDA)
15-Solina et al. 2000	15	45	Pulmonary hypertension	Group 1 milrinone Group 2 20 ppm NO Group 3 40 ppm NO (n = 15 per group)	After separation from CPB	Group 3 (40 ppm) higher RVEF compared to group 1 and 2. The milrinone group required significantly more phenylephrine in the intensive care unit
16-Sha et al 2001	75	46	Valvular cardiac surgery	Amrinone (n = 17) Milrinone (n = 15) Olprinone (n = 14)	15 minutes before end of CPB	No difference in the dosage of cathecolamines used
17-Yamaura et al 2001	33	20	Hypothermic CPB	Milrinone 0.25 μg/kg/min from CPB to 1 hour in the ICU Placebo (n = 10 per group)	Beginning of CPB until 1 hour in the ICU	Milrinone prevents gastric intramucosal acidosis and elevation in IL-6
18-Iwagaki et al 2001	8	24	Coronary revascularization	Milrinone 50 μg/kg Placebo prior to separation from CPB (n = 12 per group)	Before separation from CPB	Milrinone increase cardiac index but reduced mean arterial pressure and SVR
19-Janelle et al 2001	13	20	Coronary revascularization	Milrinone 50 μg/kg Placebo (n = 10 per group)	10 minutes before aortic cross-clamping	Milrinone patients had increased myocardial c-AMP
20-Shibata et al 2001	9	20	Coronary revascularization	Milrinone 5 μg/kg/min Placebo (n = 10 per group)	Infusion in the ICU (no bolus)	Cardiac index and HR increase in the milrinone group

(continued)

Table 1. (Continued)

Author	Reference	n	Population	Dosage	Timing	Result
21-Zabeeda et al 2001	30	50	Coronary revascularization: LIMA and radial artery flow	Group 1: nitroglycerin (n = 10) Group 2: nitroprusside (n = 10) Group 3: dobutamine (n = 10) Group 4: milrinone (n = 10) Group 5: placebo (n = 10)	Before CPB	Nitroglycerin use is the only predictor of increase flow in the LIMA and radial artery
22-Solina et al 2001	66	62	Cardiac surgery patients with pulmonary hypertension	Group 1 NO 10 ppm (n = 11) Group 2 NO 20 ppm (n = 12) Group 3 NO 30 ppm (n = 12) Group 4 NO 40 ppm (n = 12) Group 5 milrinone bolus 50 µg/kg (n = 15)	After CPB	No difference in inotropic use in all groups. NO 10 ppm is adequate
23-Feneck et al. 2001	18	120	Low CO after cardiac surgery	Milrinone 50 ?g/kg and perfusion of 0.5 ?g/kg/min Dobutamine: 10 to 20 ?g/kg/min (n = 60 per group)	Within 2 hours after CPB	Dobutamine elicits greater increases in CI. Milrinone evoked greater decreases in mean PCWP Milrinone and dobutamine: both appropriate and comparable.
24-Lobato et al. 2001	76	30	Coronary revascularization after CPB	Nitroglycerin 2 µg/kg/min Milrinone 50 µgkg/min Nitroglycerin and milrinone (n = 10 per group)	After CPB	Greater increase in internal mammary flow with milrinone
25-Mollhoff et al. 2002	77	30	Patients with LVEF < 40%	Nifedipine 0.2 µg/kg/min Milrinone 0.375 µg/kg/min (n = 15 per group)	Before CPB	Myocardial ischemia in 33% with milrinone compared to 86.6% with nifedipine
26-Kikura et al 2002	78	45	Patients undergoing coronary bypass after CPB	Milrinone 50 µg/kg and 0.5 µg/kg/min Amrinone 1.5 mg/kg and 10 µg/kg/min Placebo (n = 15 per group)	At release of aortic cross-clamping	Milrinone and amrinone increased SV and TO2 and reduced dopamine requirement
27-Kikura et al 2003	35	45	Patients undergoing coronary bypass after CPB	Milrinone 50 µg/kg and 0.5 µg/kg/min Amrinone 1.5 mg/kg and 10 µg/kg/min Placebo (n = 15 per group)	At release of aortic cross-clamping	No deterioration in platelet function and in hemostasis with milrinone and amrinone
28-Kim et al. 2003	10	30	Off-pump bypass surgery patients with atenolol	Milrinone 50 µg/kg and perfusion of 0.83 µg/kg/min X 1 hour then 0.40 Placebo (n = 15 per group)	Before off-pump bypass of the obtuse marginal (OM) artery	During OM, milrinone increased CI but with more phenylephrine

29-Hoffman et al. 2003	5	238	Congenital heart surgery neonates and young children	Low dose: 0.25 µg/kg and 0.25 µg/kg/min (n = 79) High dose: 0.75 µg/kg and 0.75 ug/kg/min (n = 73) Placebo (n = 75)	Intensive care unit: 35 hours infusion	Reduced incidence of low CO state with high dose vs low dose vs placebo (11.7% vs 17.5% vs 25.9%). 2 unrelated deaths with milrinone
30-Kwak et al 2004	79	82	Off-pump bypass surgery patients	Milrinone 0.5 µg/min/kg Placebo (n = 41 per group)	After internal mammary harvest	Milrinone prevents the reduction in cardiac index
31-Kwak et al. 2004	80	52	Off-pump bypass surgery patients	Milrinone (n = 33) 0.5 µg/min/kg Placebo (n = 29)	After internal mammary harvest	Milrinone associated with smaller reduction in CO and MVO2 during off-pump bypass
32-Maslow et al. 2004	11	34	Patients after aortic valve replacement	Epinephrine 30 ng/kg/min (n = 11) Milrinone 30 µg/kg and 0.3 µg/kg/min (n = 11) Placebo (n = 12)	After removal of aortic cross-clamping	Milrinone and epinephrine increased LVEF, RVEF and CO. No change in diastolic function.
33-Khazin et al 2004	19	90	Congenital heart surgery children with pulmonary hypertension	1-NO 2-Milrinone infusion 3-NO and milrinone (n = 30 per group)	After CPB:	NO and milrinone produce a more pronounced reduction in MPAP than milrinone alone
34-Omae et al 2004	4	140	Off-pump bypass surgery patients with mitral regurgitation 1+ to 2+	Withour MR (n = 57) With MR (n = 41) With MR + milrinone (n = 42)	After induction of anesthesia	No increase in MR and MPAP in the milrinone group during left coronary artery anastomosis
35-Lobato et al 2005	27	36	Coronary artery bypass patients	Epinephrine 0.03 µg/kg/min (n = 12) Milrinone 50 µg/kg and 0.5 µg/kg/min (n = 13) Placebo (n = 11)	During separation from CPB	No change in diastolic function with either epinephrine or milrinone No change in MPAP with milrinone
36-Shi et al 2006	24	50	Coronary artery bypass patients with LV diastolic dysfunction	Milrinone 50 µg/kg and 0.5 µg/kg/min perfusion Placebo (n = 25 per group)	Before CPB until skin closure	Milrinone increase CI, HR but no change in LV and RV diastolic function post-CPB, at 48 hours and at 6 months. More phenyephrine in the milrinone group.

AMP: adenosine monophosphate; CI: cardiac index; CO: cardiac output; CPB: cardiopulmonary bypass; ICU: intensive care unit; IL: interleukin; LIMA: left internal mammary flow; LV: left ventricular; LVEDA: left ventricular end-diastolic area; LVEF: left ventricular ejection fraction; MPAP: mean pulmonary artery pressure; MR: mitral regurgitation; MVO2: mixed venous oxygen; NO: nitric oxide; OM: obtuse marginal; PAP: pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; RV: right ventricular; RVEF: right ventricular ejection fraction; SV: stroke volume; TEE: transesophageal echocardiography; TO2: oxygen transport

of a Prospective Trial of Intravenous Milrinone for Exacerbations of chronic Heart Failure (OPTIME-CHF), sustained hypotension was noted in 10.7% vs 3.2% in the placebo group ($P < .001$).[17] Intravenous milrinone has also been shown to reduce pulmonary hypertension, pulmonary vascular resistance and increase cardiac index.[18,19] Solina and colleagues compared nitric oxide to intravenous milrinone in 45 cardiac surgical patients with pulmonary hypertension.[15] However, compared to milrinone, inhaled NO was associated with lower heart rates, higher right ventricular ejection fraction, and lower requirement for treatment with vasopressor agents. In another study, Khazin compared inhaled nitric oxide, intravenous milrinone, and their combination in 140 children with congenital heart disease and pulmonary hypertension.[20] They observed that the combination of both nitric oxide and milrinone was more efficacious in reducing pulmonary hypertension than milrinone alone.

Effects on Left Ventricular Diastolic Dysfunction

Left ventricular diastolic dysfunction is a common cause of pulmonary hypertension in cardiac surgery.[21,22] Milrinone has been shown to improve both diastolic performance in patients with congestive heart failure[23] and left ventricular compliance after CPB.[7,23,24] Based on this observation, Shi and colleagues conducted a randomized controlled trial in 50 cardiac surgical patients on the use of intravenous milrinone given after the induction of general anesthesia and during CPB in patients with left ventricular diastolic dysfunction.[25] Classification of left ventricular diastolic function was based on the Canadian consensus guidelines[26] using Doppler mitral and pulmonary venous flow velocity derived variables, mitral annulus velocities measured by tissue Doppler imaging (TDI) and color M-mode propagation velocity (Vp).[27] The use of milrinone was associated with higher CI (2.8 ± 0.8 vs 2.1 ± 0.5 L/m/m^2 $P < .0001$), stroke volume (79 ± 17 vs 70 ± 15 mL, $P = .02$), and heart rate (67 ± 8 vs 60 ± 12 beats/min, $P = .01$), and lower central venous pressure (10 ± 3 mm Hg vs 13 ± 5, $P = .01$). However, there was no significant difference between groups for pulmonary artery occlusion pressure, mean arterial pressure (MAP) and mean pulmonary arterial pressure (MPAP) during the study. Left ventricular diastolic function, based on echographic and hemodynamic criteria, was not improved with intravenous milrinone. Patients receiving milrinone required more phenylephrine in the operating room ($P = .03$). There were trends in the milrinone group for higher requirements for norepinephrine in the intensive care unit (ICU), longer intubation time, longer stay in the ICU and longer length of hospital stay, but these did not reach statistical significance. Therefore, the advantage of intravenous milrinone could have been offset by its hemodynamic side-effects. The absence of improvement in diastolic function in cardiac surgery with intravenous milrinone was also confirmed by 2 other separate clinical trials in aortic valve surgical patients[11] and in coronary revascularization patients.[28]

Effects on Internal Mammary Blood Flow

In some studies, milrinone has been reported to increase left internal mammary blood flow.[29,30] However, in comparative studies, nitroglycerin seems to be superior in that respect.[31]

Effect on Inflammatory Mediators and Hemostasis in Cardiac Surgery

Several studies have reported a eduction in CPB-related inflammatory mediators[12,32-34] and absence of clinically significant antiplatelet effect[35] or hemostatic disorders[36] with milrinone administration.

Proarrhythmia Induced by Milrinone

In the large randomized trial in acutely decompensated chronic heart failure, OPTIME chronic heart failure (CHF), atrial fibrillation and flutter was noted in 4.6% of patients in the milrinone group versus 1.5% in the placebo ($P = .004$).[17] There was also a trend in the milrinone group for more frequent ventricular tachycardia and fibrillation (1.5% vs 3.4% in the milrinone group $P = .06$)

Clinical Outcome of Milrinone in Cardiac Surgery

Although most studies have shown acute hemodynamic improvement with the use of intravenous milrinone in cardiac surgery, clinical outcomes have been addressed only in a small study. Doolan and colleagues have shown that milrinone could facilitate separation from CPB,[37] but the long-term effect was not explored and no difference in the reduction of pulmonary artery pressure was observed.

With regard to mortality, randomized controlled trials in cardiac surgery to date have not been powered or designed to correlate mortality and the use of intravenous milrinone. However, one important randomized controlled trial in the non-cardiac surgical setting deserves mention. The OPTIME-CHF trial, randomized 949 acutely decompensated chronic heart failure patients (mean LVEF of 23%) to either a 48-hour intravenous milrinone perfusion or placebo[17]; patients requiring inotropic support because of hypotension, shock, metabolic acidosis were excluded. In contrast to previous uncontrolled observations, the study did not show an advantage in terms of duration of hospitalization or death in the group receiving intravenous milrinone. Moreover, during hospitalization, milrinone patients had more adverse events (12.6% vs 2.1%, $P < .001$), atrial fibrillation and flutter (4.6% vs 1.5%, $P = .004$) and sustained hypotension (10.7% vs 3.2%, $P < .001$).[36] A post-hoc analysis of the trial comparing patients with or without ischemic cardiomyopathy revealed that the end-point of death and rehospitalisation was higher in patients with ischemic cardiomyopathy receiving intravenous milrinone (42% vs 36%, $P = .01$).[38] Because hypotension and proarrhythmia can be significant problems in cardiac surgery, it appears pertinent to explore alternative strategies, such as inhaled milrinone.

Is Cardiac Index the Best Primary Endpoint?

Although cardiac index is thought to be a good hemodynamic surrogate endpoint in cardiac surgery, most large scale studies have confirmed that pulmonary arterial pressure represents the most predictive hemodynamic variable in regard to postoperative outcome. In fact, pulmonary hypertension has been systematically associated with increased morbidity and mortality in cardiac surgery.[39-43]

In this respect, a recent study has suggested that relative pulmonary hypertension, defined as the ratio of MAP/ MPAP, could also represent an important predictive variable in cardiac surgery.[44] Robitaille and colleagues evaluated the prognostic value of the hemodynamic profile as a predictor of complications after cardiac surgery. A total of 1439 consecutive adult patients having undergone a cardiac surgical procedure during 1999 were included (96% of the population operated in 1999).[44] Hemodynamic parameters were collected before the beginning of the procedure after the induction of general anesthesia and were then analyzed to assess their ability to predict total mortality or a combined end-point of hemodynamic complications that included death, unexpected cardiac arrest, administration of vasoactive drugs for more than 24 hours postoperatively or the insertion of an intra-aortic balloon pump (IABP) not inserted preoperatively. Overall there were 50 deaths and 33 (66%) were secondary to hemodynamic complications. Patients with hemodynamic complications required more preoperative vasoactive drugs (4% vs 1%, $P < .001$), had more preoperative intra-aortic balloon pumping IABP (10% vs 3%, $P< 0.001$) and more frequent difficult separation from bypass (DSB) (84% vs 55%, $P< .001$). The cardiac index of those developing hemodynamic complications was 2.1± 0.6 compared to 2.2 ± 0.6 in those free of complications ($P = .009$, statistically significant but not clinically significant difference). After multiple stepwise logistic regression analysis, the only hemodynamic variable associated with this primary end-point was relative pulmonary hypertension defined using the MAP/MPAP ratio (odds ratio1.3, [OR], confidence interval [CI]:1.1-1.5). The MAP/MPAP ratio (normal value > 4), as an index of the severity of pulmonary hypertension, has also been used in risk stratification in cardiac surgery when measured either before[39] or after induction of anesthesia.[45] From these studies, one could hypothesize that the reduction in pulmonary artery pressure, a well known prognostic factor in cardiac surgery[42] instead of an increase in cardiac index, could represent a better surrogate endpoint in cardiac surgery. Further studies are, however, needed to validate this hypothesis.

Pulmonary Hypertension in Cardiac Surgery

Pulmonary hypertension is an hemodynamic variable associated with increased morbidity and mortality in cardiac surgery.[39-43] The evaluation of pulmonary hypertension can be done by measuring mean, systolic, and diastolic pulmonary arterial pressures, as well as by calculating pulmonary vascular resistance and the transpulmonary gradient.[46] Pulmonary hypertension is usually defined as a MPAP greater than 25 mm Hg at rest or a MPAP greater than 30 mm Hg during exercise. Ratios relating MAP to MPAP (MAP/MPAP), or systemic to pulmonary vascular resistances, have also been used to quantify pulmonary

hypertension in adults[47-49] and in patients with congenital heart disease.[50] Given the same MPAP, a patient with lower systemic arterial pressure has relatively more severe pulmonary hypertension. The use of the MAP/MPAP ratio is particularly relevant in situations involving general anesthesia or sedation, during which a reduction of MAP and MPAP is frequently observed, but in which the MAP/MPAP ratio tends to remain unchanged.[44,51] As mentioned previously, in a retrospective study involving 1439 patients,[44] Robitaille and colleagues observed that the MAP/MPAP ratio was lower in those who died (3.16 ± 1.36 vs. 3.92 ±1.43, $P = .0002$) and in those who had hemodynamic complications, (3.3 ± 1.33 vs. 4.04 ± 1.42, $P < .0001$). This study suggested that the MAP/MPAP ratio is a useful predictor of the composite index of mortality and hemodynamic complications in cardiac surgery. Chagnon and colleagues conducted a retrospective analysis of 243 consecutive patients having undergone a cardiac surgical procedure from 2003 to 2004 to confirm the findings of the previous study and explore the prognostic value of transesophageal echocardiography (TEE)–related variables. Demographic, perioperative variables, "Swan-Ganz"–derived hemodynamic profile and a standard sequence of cardiac images to evaluate systolic and diastolic function (using multiplane TEE) were obtained after the induction of general anesthesia before sternotomy. The primary endpoint consisted of a composite index of death, resuscitated cardiac arrest or the use of vasoactive support for more than 24 hours postoperatively. They observed hemodynamic complications in 49 patients (20%) defined by the composite index. These patients had higher Parsonnet scores and body mass index, more complex surgeries and left ventricular dilatation, longer bypass and aortic cross-clamping time, more frequent difficult separation from CPB, lower MAP/MPAP, lower left ventricular fractional area change and higher regional wall motion score index (RWMSI) . In the univariate analysis, the only significant hemodynamic and echocardiographic variables were the MAP/MPAP ratio (3.38 ± 1.51 vs 3.76 ± 1.17; OR 0.75, CI 0.56-1.00, $P = .0524$) and the RWMSI (OR 2.26, CI 1.17-4.35, $P = .0153$). Multiple stepwise logistic regression analysis showed that the only 3 independent predictors of postoperative hemodynamic complications were duration of CPB (128 ± 57 vs 90 ± 42 min; OR 1.02, CI 1.01-1.02, $P < .0001$), aortic cross-clamp time (87 ± 44 vs 60 ± 40 min; OR 1.02, CI 1.01-1.02, $P < .0002$), and difficult separation from CPB (82% vs 45%; OR 5.47, CI 2.52-11.9, $P < .0001$). The only preoperative variables that could potentially be modulated before cardiac surgery were the severity of pulmonary hypertension and left ventricular dysfunction and could potentially decrease the incidence of difficult weaning from bypass.

In addition, pulmonary hypertension can be exacerbated after CPB due to the reperfusion syndrome. Cardiopulmonary bypass induces a systemic inflammatory response that affects all organ systems. During CPB, blood flow is diverted from the right atrium to the CPB pump, goes through an oxygenator membrane, and is pumped back into the aorta, and thus the lungs are minimally perfused during CPB. At separation from CPB, the lungs are reperfused and experience ischemia-reperfusion injury caused by exposure to large amounts of oxygen free radicals. Because of the contact of the blood elements with the non-physiologic surface of the bypass circuit, neutrophils and platelets are activated and contribute to pulmonary damage, which triggers endothelial dysfunction after CPB.[52]

This extensive contact between blood and artificial surfaces during CPB is known to activate a range of mediators, including the complement cascade, thrombin, oxygen free radicals and vasoactive mediators, resulting in the activation of platelets and neutrophils. The physiologic alterations after CPB were recognized early after the development of CPB in the 1950s. The post-pump syndrome is characterized by an increase in pulmonary capillary permeability, leading to decreased oxygenation, increased alveolar-arterial oxygen gradient, decreased pulmonary compliance and an increased pulmonary vascular resistance.[53,54] Among the most important repercussions of the inflammatory cascade are those on the pulmonary vasculature. CPB can cause or exacerbate pulmonary hypertension.[52,55] The diversion of pulmonary blood flow during CPB also causes potential ischemia-reperfusion injury of the lung.[52,55] The endothelin system is also activated during cardiopulmonary bypass (CPB) in patients undergoing cardiac surgery.[56-61] Increased ET-1 levels during and after CPB are associated with pulmonary and systemic vasoconstriction, resulting in increased pulmonary arterial pressure and vascular resistance, and reduced myocardial contractility.[56-61] ET-1 levels correlate with the duration of CPB as the increase is larger during longer bypass time. The surge in ET release during

and after CPB may contribute to the ischemia-reperfusion injury and systemic inflammatory response altering pulmonary endothelial function, which leads to pulmonary hypertension and DSB.[58,62]

After CPB, the increased pulmonary vascular resistance associated with functional alteration of the endothelial cells can lead to an increase in right ventricular work. Right ventricular dysfunction after CPB carries a poor prognosis, with a perioperative mortality ranging from 44% to 86%.[63] Several strategies to prevent this syndrome and reduce pulmonary hypertension have been explored. Rescue therapy for pulmonary hypertension include oral sildenafil,[64] intravenous vasopressor/inotropic drugs such as epoprostenol/iloprost, inhaled agents such as prostacyclin,[65] milrinone,[48] and nitric oxide,[66] and mechanical support using ventricular assist devices. None of the pharmacological treatments used are currently approved for this indication.

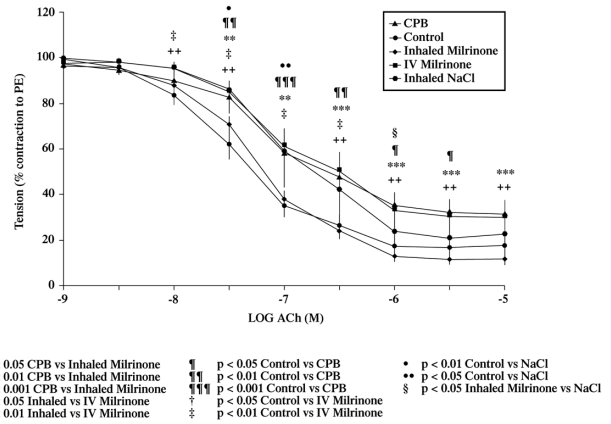

Figure 1 Rings of porcine pulmonary with endothelium. *X-axis*, Log acetylcholine (mol/L); *Y-axis*, tension (percent contraction to phenylephrine); *PE*, phenylephrine. Data are expressed as means ± SEM. **P* < .05, CPB vs inhaled milrinone; ***P* < .01, CPB vs inhaled milrinone; ****P* < .001, CPB vs inhaled milrinone; *P* < .05, inhaled vs intravenous milrinone; *P* < 0.01, inhaled vs intravenous milrinone; ¶*P* < .05, control vs CPB; ¶¶*P* < .01, control vs CPB; ¶¶¶*P* < .001, control vs CPB; †*P* < .05, control vs intravenous milrinone; ‡*P* < .05, control vs intravenous milrinone. (With permission from Lamarche Y, Malo O, Thorin E, et al. Inhaled but not intravenous milrinone prevents pulmonary endothelial dysfunction after cardiopulmonary bypass. *J Thorac Cardiovasc Surg*. 2005;130:83-92.)

Studies on Inhaled Milrinone

Pulmonary artery pressure was reduced in a porcine model of CPB given inhaled milrinone before CPB. This reduction in MPAP was secondary to preservation of pulmonary arterial endothelial function and increased cAMP content in pulmonary artery cells, favoring vasodilatation even in the setting of a reperfusion injury after CPB[67] (Figures 1, 2). The reduction in pulmonary artery pressure and the reperfusion injury sparing effect of inhaled milrinone was not observed with intravenous milrinone. Similar findings were also observed in the same animal model using inhaled prostacyclin.[68] These approaches could represent potential strategies for reducing the pulmonary reperfusion syndrome and consequently post-CPB pulmonary hypertension.

Only 2 reports addressing the role of inhaled milrinone in cardiac surgery have been published so far.[48,69] In the first study, an open label trial of 20 patients, 9 patients received incremental doses of inhaled milrinone ranging from 0.25 to 1 mg/mL and 11 received a combination of inhaled milrinone (1 mg/mL) and inhaled epoprostenol (10 µg/mL) after separation from CPB in the cardiothoracic intensive care unit. The first part of that trial showed a dose response effect of incremental concentrations of inhaled milrinone with a decrease in MPAP and in pulmonary vascular resistance in the 1 mg/mL group. Systemic hypotension did not develop. The hemodynamic parameters of patients treated with inhaled milrinone returned to baseline within 20 minutes after the end of the inhalation period. Addition of inhaled epoprostenol to milrinone enhanced the reduction of pulmonary vascular resistance (Figure 3), increased wedge pressures but also the PaO_2, stroke volume, SvO_2 with a reduction in oxygen extraction. The combination of the 2 drugs prolonged the duration of the effects by more than 20 minutes after cessation of the treatment. In the second study, inhaled milrinone was given to 18 heart transplant recipients.[69] The MPAP, transpulmonary gradient and pulmonary vascular resistance decreased only in patients with pulmonary hypertension, defined as a MPAP above 30 mm Hg (Figure 4). No systemic hypotension was observed. The dose was 2 mg based on intravenous milrinone loading doses used in heart transplantation. The magnitude of the effect was similar to that of previous studies. However, in both studies, intraoperative use and the timing of inhaled milrinone were not explored.

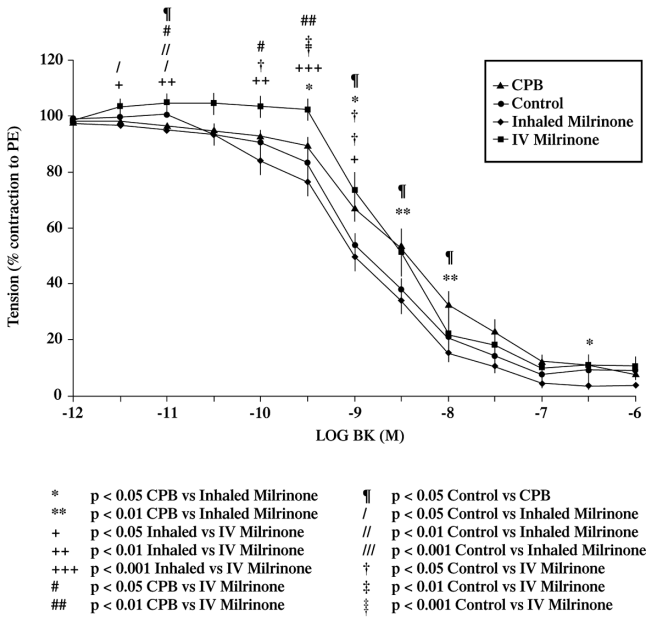

Figure 2. Rings of porcine pulmonary with endothelium. *X-axis*, Log bradykinin (mol/L); *Y-axis*, tension (percent contraction to phenylephrine); *PE*, phenylephrine. Data are expressed as means SEM. **P* < .05, CPB vs inhaled milrinone; ***P* < .01, CPB vs inhaled milrinone; *P* < .05, inhaled vs intravenous milrinone; *P* < .01, inhaled vs intravenous milrinone; *P* < .001, inhaled vs intravenous milrinone; #*P* < .05, CPB vs intravenous milrinone; ##*P* < .01, CPB vs intravenous milrinone; ¶*P* <.05, control vs CPB; /*P* < .05, control vs inhaled milrinone; //*P* < .01, control vs inhaled milrinone; ///*P* < .001, control vs inhaled milrinone; †*P* < .05, control vs intravenous milrinone; ‡*P* < .01, control vs intravenous milrinone; †††*P* < .001, control vs intravenous milrinone. (With permission from Lamarche Y, Malo O, Thorin E, et al: Inhaled but not intravenous milrinone prevents pulmonary endothelial dysfunction after cardiopulmonary bypass. *J Thorac Cardiovasc Surg*. 2005;130:83-92.)

In a human study involving 73 high-risk patients with a mean preoperative Parsonnet score of 27 ± 14, Lamarche and colleagues observed that preemptive administration of inhaled milrinone before CPB (n = 30), compared to administration after CPB, was associated with a lesser rate of re-initiation of CPB (9 vs 1 *P* = .021), in this high risk group of patients. Lower pulmonary artery pressure and no worsening in left ventricular function measured with TEE using fractional area change and regional wall motion score index (RWMSI) were found (JTCVS accepted pending revision). Administration of milrinone before CPB, through a more uniform distribution and penetration in the lung parenchyma could protect the pulmonary vasculature during weaning from CPB when ischemia-reperfusion injury occurs. This may explain why patients receiving milrinone before CPB had lower MPAP after separation from CPB. These findings were not observed when the administration of the drug occurred after CPB. The administration of milrinone before CPB could be advantageous as the drug can be distributed in mechanically ventilated lungs, without any significant atelectasis before CPB.

In addition, as demonstrated in the animal model,[67] inhaled milrinone could prevent the post CPB reperfusion injury associated with pulmonary hypertension which could explain the lower MPAP values and the improved left ventricular function after separation from CPB. Our clinical experience also supports use of inhaled milrinone and we have observed improvement in both systolic and diastolic function using this new approach (Figure 5). Nitric oxide and epoprostenol are other inhaled agents that can be used in patients to treat pulmonary hypertension in cardiac surgery.[51,65,70-72] However, in clinical practice, nitric oxide is more complex to install, more expensive, and toxic metabolites have to be monitored when used continuously. On the other hand, inhaled milrinone is less expensive, is readily available in any operating room and needs no special preparation, as opposed to inhaled epoprostenol, as it only requires a simple nebulizer for administration. We have been using simple nebulizers[67] but have recently adopted the use of ultrasonic nebulizers for their simplicity of use and the absence of a secondary oxygen flow (Figure 6). These issues make inhaled milrinone an attractive option in a cardiac operating room.

Conclusion

In summary, inhaled milrinone is an interesting approach for reducing pulmonary hypertension and preventing the reperfusion syndrome after CPB. It could therefore represent a strategy to facilitate separation from CPB and potentially reduce morbidity and mortality in cardiac surgery. Several issues must be clarified including the ideal timing, the duration of the effect, the optimal dosages, the maintenance of administration and the advantages of the inhaled mode compared to the intravenous route. Future randomized controlled trials will seek to answer these questions.

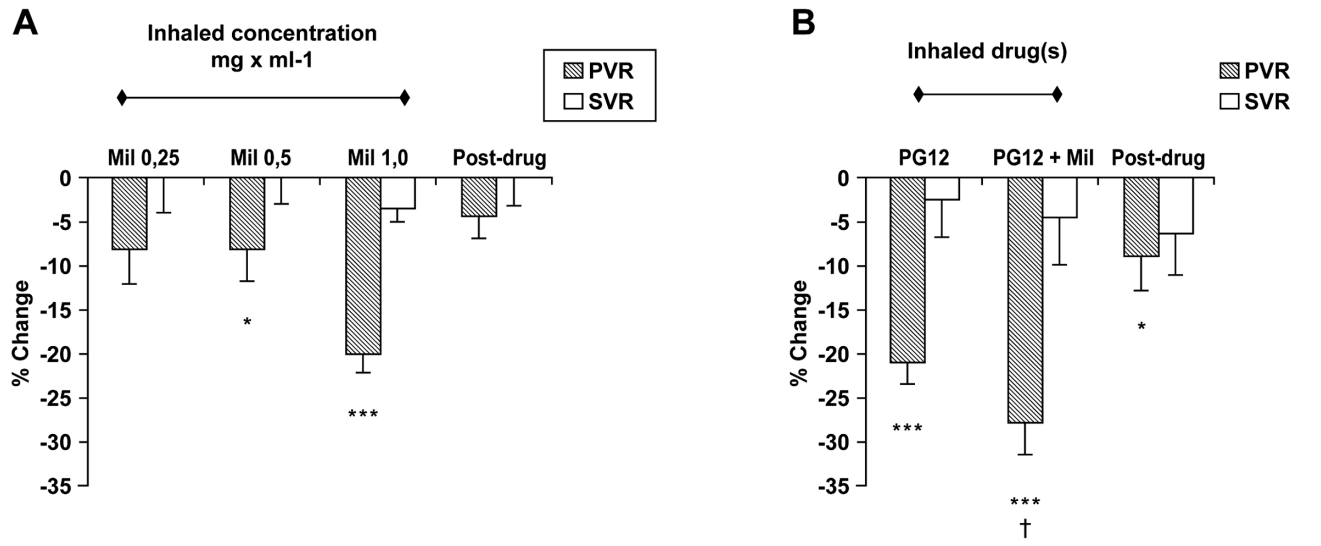

Figure 3. Percentage changes in pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR) during inhalation of incremental concentrations of milrinone (mil) (0.25; 0.5 and 1.0 mg/ mL) and 20 min postinhalation (**A**) and during inhalation of prostacyclin (PGI2) (10 g/mL) and PGI2 (10 g/mL) milrinone (mil) (1.0 mg/mL) and 20 min postinhalation (**B**). * $P < .05$ control vs inhaled milrinone .25; .5 and 1.0 mg/mL and 20 min postinhalation or inhaled PGI2 (10 g/mL), PGI2 (10 g/mL) mil (1.0 mg/mL), and 20 min postinhalation. *** $P < .001$ control vs inhaled milrinone 0.25, 0.5, and 1.0 mg/mL and 20 min postinhalation or inhaled PGI2 (10 g/mL), PGI2 (10 g/mL) mil (1.0 mg/mL) and 20 min postinhalation. † $P < .05$ inhaled PGI2 (10 g/mL) vs PGI2 (10 g/mL) mil (1.0 mg/mL). (With permission from Haraldsson A, Kieler-Jensen N, Ricksten SE. The additive pulmonary vasodilatory effects of inhaled prostacyclin and inhaled milrinone in postcardiac surgical patients with pulmonary hypertension. *Anesth Analg*. 2001;93:1439-1445.)

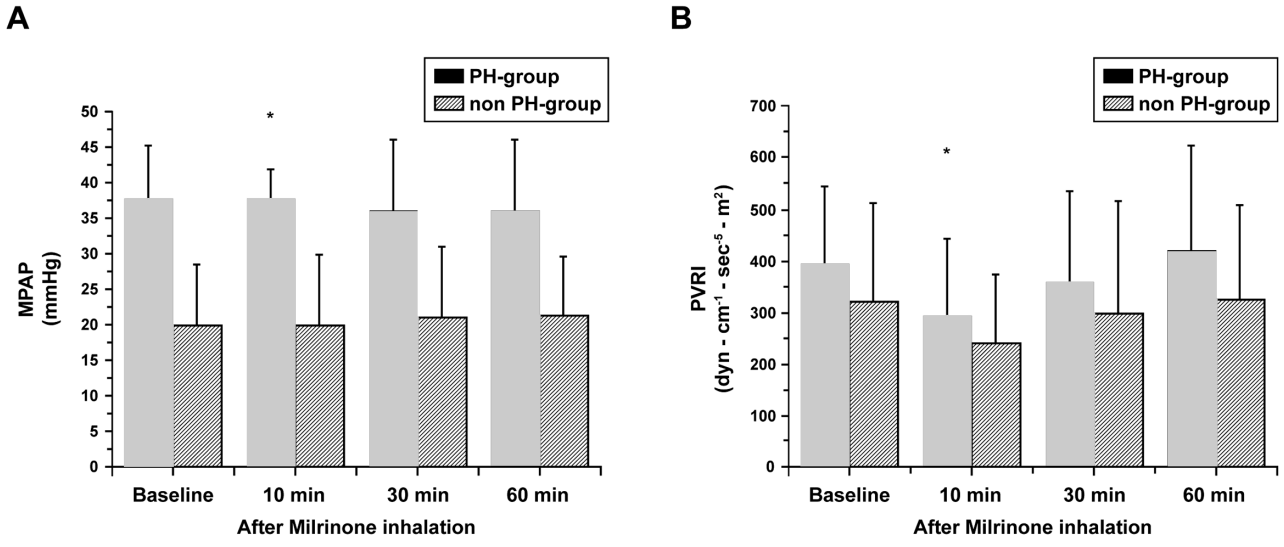

Figure 4. **A:** Effect of milrinone-inhalation on mean arterial pressure in patients with ($n = 9$) and without ($n = 9$) pulmonary hypertension; *$P < .05$ compared to baseline. **B:** Effect of milrinone-inhalation on pulmonary vascular resistance index in patients with ($n = 9$) and without ($n = 9$) pulmonary hypertension; *$P < .05$ compared to baseline. (With permission from Sablotzki A, Starzmann W, Scheubel R, et al: Selective pulmonary vasodilation with inhaled aerosolized milrinone in heart transplant candidates: la vasodilatation pulmonaire selective avec l'inhalation de milrinone en aerosol chez des candidats a la greffe cardiaque. *Can J Anaesth*. 2005;52:1076-1082.)

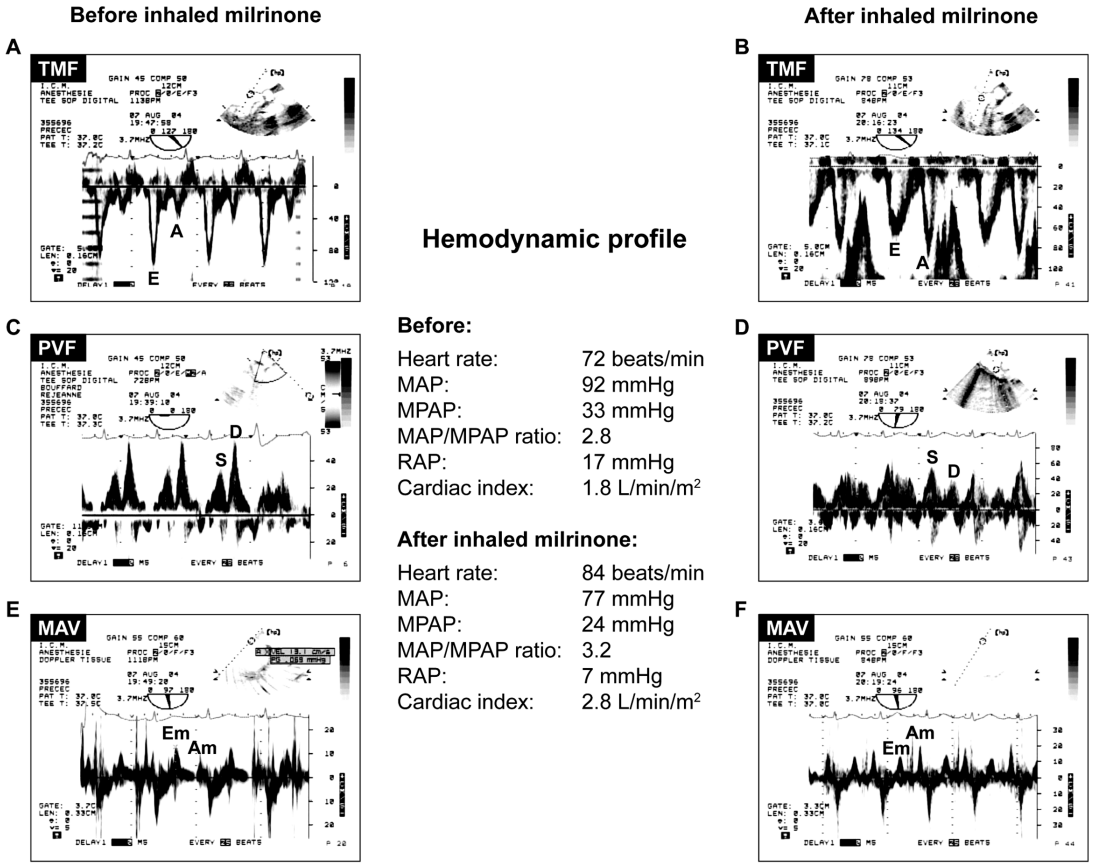

Figure 5. Inhaled milrinone in a patient in cardiogenic shock Parsonnet 51. A 73-year-old woman in cardiogenic shock scheduled for CABG. After inhaled milrinone, a reduced E/A ratio of transmitral flow (TMF) (A-B), increased S/D ratio of pulmonary venous flow (PVF) (C-D) and changes mitral annular velocity (MAV) are consistent with improvement of left ventricular diastolic function. In addition, reduction in mean pulmonary artery pressure (MPAP), increased MAP/MPAP ratio, reduction in right atrial pressure (RAP) and increases in the cardiac index were observed. She was weaned successfully from cardiopulmonary bypass.

Figure 6. Ultrasonic nebulizer (Aeroneb Professional Nebulizer System, Aerogen Ltd, Galway, Ireland) used at the Montreal Heart Institute.

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