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Pilot Randomized Controlled Trial of Inhaled Milrinone in High-Risk Cardiac Surgical Patients

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Abstract

Background: Pulmonary hypertension is a major cause of mortality and morbidity in patients undergoing valvular and complex heart surgery. Inhaled milrinone has been used for the treatment of pulmonary hypertension, but its safety and effects compared with a placebo on hemodynamics and ventricular function have not been studied in patients undergoing high-risk valvular surgery.

Methods: Twenty-one high-risk cardiac surgical patients with preoperative pulmonary hypertension were randomized in a double-blind study to receive inhaled milrinone or placebo. The inhalation occurred after the induction of anesthesia and before the surgical incision and cardiopulmonary bypass. The effects on ventricular function were evaluated by means of pulmonary artery catheterization and transesophageal echocardiography. The primary outcome variable was the systemic mean arterial pressure.

Results: There were 8 men and 13 women (mean age 71 ± 6 years) with a mean Parsonnet score of 32 ± 9 who underwent a total of 17 complex procedures and 6 reoperations. There were no significant changes in mean arterial pressure throughout the study. A reduction in pulmonary vascular resistance ($p = 0.0458$) was observed in the inhaled milrinone group, but the change in mean pulmonary artery pressure was not significant ($p = 0.1655$). Right ventricular end-diastolic area ($p = 0.0363$) and right atrial transverse diameter ($p < 0.0001$) increased in the control group, but not with inhaled milrinone. No significant side effects occurred in the inhaled milrinone group.

Conclusion: In this high-risk cardiac surgery cohort, the use of inhaled milrinone was not associated with systemic hypotension but with a reduced pulmonary vascular resistance and prevention of the increase in right-sided cavity dimensions.

Keywords: Cardiac surgery; Milrinone; Transesophageal echocardiography; Cardiopulmonary bypass; Outcome; Pulmonary hypertension

Introduction

Pulmonary hypertension is a major cause of mortality and morbidity in patients undergoing cardiac surgery [1] Several conditions increase the risk of developing perioperative pulmonary hypertension, including pre-existing pulmonary hypertension, mitral stenosis or regurgitation, left ventricular (LV) dysfunction pulmonary disease and cardiopulmonary bypass (CPB) [2]. Studies have suggested that milrinone may be beneficial in the treatment of pulmonary hypertension in cardiac surgery [3,4]. However, intravenous milrinone can be associated with systemic hypotension, [5] increased vasoactive drug requirements [6], morbidity [7] and mortality in ischemic cardiomyopathy [8]

The use of the inhaled route for milrinone (iMil) has been described in several animal [9-15], human studies [16-22] and case reports [23-26]. As an alternative to inhaled nitric oxide and inhaled prostacyclin, inhaled milrinone (iMil) is also less expensive and does not require a complex set-up and monitoring of toxic metabolites. Furthermore, iMil is readily available in operating rooms and needs no special preparation, as opposed to inhaled prostacyclin. In addition, iMil before CPB has been shown to be superior to an intravenous administration in reducing the pulmonary reperfusion syndrome [10], preventing pulmonary arterial endothelial dysfunction [12,13] and improving oxygenation in a porcine model [10]. Only two open-label studies described the use of iMil after cardiac surgery and in heart transplant candidates undergoing catheterization [16,17], with no significant side effects.

However, in these studies, the timing of administration was constant, the effect on ventricular function using combined hemodynamic and echocardiographic monitoring not evaluated and the investigators were not blind to the effect of iMil. The primary hypothesis of our study was that the administration of milrinone through nebulization before CPB would not be associated with significant systemic hypotension. Our secondary hypothesis was that iMil administered before CPB is better than placebo in improving pulmonary hemodynamics and both LV and right ventricular (RV) function.

Methods

Study Population

After approval by our local research and ethics committees and with permission from Health Canada, informed consent was obtained from 22 patients with pulmonary hypertension undergoing cardiac surgery with CPB. Patients were considered to have pulmonary hypertension if the systolic pulmonary artery pressure (SPAP) was greater than 30 mmHg or the mean pulmonary artery pressure (MPAP) above 25

mmHg, as measured during the preoperative period or estimated by using Doppler echocardiography. This was confirmed after insertion of a pulmonary artery catheter and before induction of general anesthesia. Patients with severe LV dysfunction (LV ejection fraction of less than 30%) were excluded. Other exclusion criteria were the presence of contraindications to transesophageal echocardiography (TEE), including esophageal disease or unstable cervical spine.

Treatment Protocol

Patients were premedicated with 1 to 2 mg of lorazepam administered orally 1 hour before the operation, as well as 0.1 mg/kg of morphine administered intramuscularly before being taken to the operating room. Additional midazolam was administered (0.01-0.05 mg/kg intravenously) in the operating room as needed for patient comfort. Usual monitoring was installed, including a 5-lead electrocardiogram, pulse oximeter, peripheral venous line, radial arterial line, a 15-cm 3-lumen catheter (CS-12703, Arrow International Inc., Reading, CA), and thermodilution pulmonary artery catheter (Swan-Ganz catheter 7.5F; Baxter Healthcare Corporation, Irvine, CA). Anesthesia was induced with 0.04 mg/kg midazolam and 1 μg/kg sufentanil, and muscle relaxation was achieved with 0.1 mg/kg pancuronium. After tracheal intubation, anesthesia was maintained with 1 μg/kg/hr sufentanil and 0.04 mg/kg/hr midazolam. No anesthetic gases were used for the induction. Minute ventilation was adjusted to maintain end-tidal carbon dioxide between 30 and 40 mmHg with an infrared carbon dioxide analyzer. Transesophageal echocardiography (Vivid 7 imaging system, GE Healthcare, Amersham, Sweden) was performed after induction of general anesthesia. Intravenous fluids (0.9% normal saline) were administered according to estimated insensible losses of 7 ml/kg/hr during the surgery and titrated according to blood pressure and central venous pressure (CVP). A decrease in mean arterial pressure (MAP) below 60 mmHg was treated by fluids administration in the presence of a low CVP or by the use of vasopressors according to a predetermined protocol [27]. In case of low cardiac output (CO) with reduced contractility documented using TEE, the anesthesiologist could use intravenous milrinone at his discretion. Postoperative management in case of pulmonary hypertension included intravenous nitroglycerin and milrinone and, in more severe cases, inhaled nitric oxide or inhaled prostacyclin. During CPB, blood cardioplegia was used in all patients. Induction and maintenance of cardioplegia were cold to tepid (15 to 29° Celsius). The blood to crystalloid ratio was 4:1. The pump flow was adjusted to obtain an output of 2.2 L/min/m² of body surface area. The pump flow was reduced to 0.5 L/min for aortic clamping and unclamping. The pumps used for all patients were SIII (Stockert, Munchen, Germany) roller pumps and the oxygenators were Sorin Monolyth (Mirandola, MO, Italy). For coronary artery bypass procedures, temperature was allowed to drift to 34°C. Valve and complex procedures were done with temperatures of 32-34°C. Selective antegrade and retrograde cerebral perfusion were used on a case by case basis. Weaning from CPB was attempted after systemic temperature (central and vesical) was > 36°C using a predetermined protocol [27].

Drug Administration Protocol

Randomization was done according to a list of computerized random numbers generated by the Montreal Heart Institute Coordinating Center and assignment to study treatment was directly transmitted to the pharmacist the day before the surgery. The investigator had no access to the randomization list. The study drug was prepared by the pharmacist and delivered to the operating room wrapped up in an opaque paper to maintain blinding. Patients were equally divided into 2 groups to receive either iMil or placebo in a double-blind randomized

manner. Inhaled milrinone (Primacor, Sanofi-Synthelabo Canada Inc., Markham, ON, Canada) or the placebo (0.9% saline) were administered through the endotracheal tube after the induction of anesthesia once baseline hemodynamic profiles and TEE exam were completed [28]. Five milligrams (1 mg/mL) were administered, resulting in a dose ranging from 50-80 μg/kg, over 5 minutes. The study drug and the placebo were administered through a jet nebulizer (Ref 8901; Salter Labs, Arvin, CA) attached to the inspiratory limb of the ventilator near the endotracheal tube with a bypass flow of oxygen at 10 L/min, as previously described [28].

Data Collection

At the time of randomization, demographic, diagnostic (New York Heart Association (NYHA) class, Parsonnet score, comorbidities, LV ejection fraction) and therapeutic (medication, type of surgery, reoperations) information was obtained for every patient. Complex surgery was defined as a combination of valve or aortic surgery and coronary procedure or reoperative surgery. Hemodynamic values were indexed for patient body surface area and obtained in the awake state before induction of anesthesia to confirm the presence of pulmonary hypertension, after induction of anesthesia (baseline or T1), at the end of nebulization (T2), 20 minutes after the end of nebulization before CPB (T3) and after CPB during chest closure (T4). The measured hemodynamic parameters included heart rate (HR), systemic arterial pressure (SAP), MAP, CVP, pulmonary capillary wedge pressure (PCWP), SPAP, MPAP and diastolic pulmonary artery pressure (DPAP). Systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) was calculated using the standard formula. Cardiac output was assessed by using the thermodilution technique with 3 injections of room temperature dextrose 5% (10 mL) at end-expiration. All TEE were performed by 2 anesthesiologists with more than 15 years of experience and with National Board Certification. All TEE exams were reviewed offline by a cardiologist expert in echocardiography who was blinded to the allocation group. The exam was obtained after induction (T1), at the end of nebulization (T2), before CPB (T3) and after CPB (T4). The TEE examination included a mid-esophageal, 4-chamber view, a short-axis transgastric view at the mid-papillary level, and color flow Doppler imaging of all the valves to detect any unsuspected significant valvular disease. All 2-dimensional images in which the LV and RV endocardial border could not be traced adequately by using Schnittger criteria [29] were excluded. The RV function was evaluated using the 4-chamber view according to published guidelines [30]. The following measures were also obtained from the 4-chamber view: the maximal transverse dimensions of the right atrium (RADt) and left atrium (LADt), the right ventricular end-diastolic area (RVEDA), right ventricular end-systolic area (RVESA), the RV fractional area change (RVFAC) in % calculated as (RVEDA-RVESA)/RVEDA and the tricuspid systolic annular plane excursion (TAPSE). The LV function was evaluated using the 4-chamber view and the transgastric short-axis view. LV end-diastolic area (LVEDA), LV end-systolic area (LVESA) and the LV fractional area change (LVFAC) in % calculated as (LVEDA - LVESA)/LVEDA were obtained from both views. Measures were averaged over three consecutive cycles and standardized to end-expiration. The inter-observer variability for area measurements was 2.9 ± 2.0% (absolute difference) with an intra-class correlation coefficient of 0.95.

Outcome Measures

The primary outcome measure was the change in MAP. Secondary outcomes were the changes in MPAP, PVR and PVR/SVR reduction, RV and LV areas. We were also interested in exploring the impact of iMil on weaning from CPB support, vasopressors use > 24 hours, postoperative

atrial fibrillation, intensive care unit (ICU) and hospital stays and mortality. Difficult separation from bypass was defined as SAP < 80 mmHg, confirmed by central measurement (femoral or aortic); DPAP or PCWP > 15 mmHg during progressive weaning from CPB; and the use of inotropic or vasopressive support (norepinephrine > 4 μg/min, epinephrine > 2 μg/min, dobutamine > 2 μg/kg/min) for at least 1 hour, intra-aortic balloon pump (IABP) requirement or reinitiation of CPB [28,31].

Statistical Analysis

Patient characteristics were expressed as mean ± standard error (SE) or simple frequencies and percentages. Comparisons of continuous variables between groups were performed with the Student t-test for normally distributed variables (original or after appropriate transformations) or with the Wilcoxon test for non-normally distributed variables. Due to very low power, categorical variables were not compared between or within groups. One-way analysis of variance (ANOVA) on repeated measurements were used to study variations over time within each groups. Two-way analysis of

co-variance (ANCOVA) adjusted for baseline values (T1) were used to compare groups at T2, T3 and T4. Sample size was calculated for a power of 80% and a 1-sided α error value of 0.05. Assuming a MAP of 75 mmHg in the placebo group, a common standard deviation of 13 mmHg, 11 patients per group would be sufficient to detect a 15 mmHg reduction in MAP in the iMil group. Statistical analyses were done with the computer software SAS version 9.1 (SAS Institute Inc., Cary, NC). A P value < 0.05 was considered statistically significant.

Results

A total of 22 patients were recruited over a ten month period. One patient was excluded because the pulmonary artery catheter did not confirm the presence of pulmonary hypertension; therefore, a total of 10 controls and 11 iMil were studied. Patients' characteristics for each group are listed in Table 1. For all patients, the mean age was 71 ± 6 years and there were 8 men and 13 women with a mean Parsonnet score of 32 ± 9. A total of 17 complex procedures and 6 reoperations were performed. The pre-induction hemodynamic variables (not shown) were similar between the groups for the HR, SAP, MAP, CVP, PCWP

Characteristics	Control (n = 10)	Inhaled Milrinone (n = 11)
Age (yrs)	71 ± 1	70 ± 3
Sex		
Male	3 (30%)	5 (45%)
BMI (kg/m²)	27 ± 2	26 ± 1
NYHA class		
1	0	0
2	2 (20%)	0
3	8 (80%)	10 (91%)
4	0	1 (9%)
Parsonnet score	32 ± 3	32 ± 3
Current smoking	2 (20%)	0
Type of surgery		
Isolated valve	4 (40%)	0
Multiple valves	0	4 (36%)
Complex	5 (50%)	6 (54%)
Other	1 (10%)	1 (9%)
Reoperation**s**	2 (20%)	4 (36%)
Cardiac disease		
Prior myocardial infarction	1 (10%)	2 (18%)
Congestive heart failure	8 (80%)	9 (82%)
Comorbidities		
Hypertension	7 (70%)	7 (64%)
Diabetes mellitus	4 (40%)	5 (45%)
Peripheral vascular disease	5 (50%)	0
Renal failure	3 (30%)	3 (27%)
COPD	3 (30%)	2 (18%)
Coronary artery disease	6 (60%)	4 (36%)
Drug therapy at admission		
Coumadin	4 (40%)	5 (45%)
Heparin	2 (20%)	1 (9%)
Nitrates	0	1 (9%)
Calcium-channel antagonists	2 (20%)	2 (18%)
Beta-blockers	7 (70%)	5 (45%)
ACE inhibitors	4 (40%)	4 (36%)
Digoxin	3 (30%)	2 (18%)
Diuretics	6 (60%)	3 (27%)
Salicylates	3 (30%)	4 (36%)
Statins	7 (70%)	4 (36%)
Left ventricular ejection fraction (%)	55 (50-60)*	58 (40-65)*
Duration of surgery (min)		
CPB	119 ± 13	123 ± 7
Aorta clamping	88 ± 10	97 ± 9

Table 1: Baseline Characteristics of the Study Population

ASD, atrial septal defect; AVR, aortic valve replacement; ACE, angiotensin-converting enzyme; BMI, body mass index; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; COPD, chronic obstructive pulmonary disease; MV, mitral valve; MVR, mitral valve replacement; NYHA, New York Heart Association; TV, tricuspid valve. *1st and 3rd interquartile range.

and CO. Before the induction of anesthesia, the SPAP (66 ± 20 *vs.* 46 ± 13 mmHg, $p = 0.0121$) and MPAP (45.5 ± 12 *vs.* 33 ± 8 mmHg, $p = 0.0047$) were higher in the iMil group compared to the control group.

Within Groups Comparison

Hemodynamic Measurements: Hemodynamic evolutions are shown in table 2 for the control and iMil separately. There were no changes over time for MAP in the iMil group ($p = 0.3781$) and in the control group ($p = 0.9478$). In patients receiving iMil, there were changes over time for HR ($p = 0.0174$) and SVR ($p = 0.0465$).

Echocardiographic Measurements: Sequential echocardiographic changes are shown in **Erreur ! Source du renvoi introuvable.** Figure 1 for the control and iMil groups separately. A total of 66 (83%) 4-chamber views for RV area were analyzed; 58 (73%) 4-chamber views and 49 (61%) transgastric views were used for LV area measurements. No changes over time were observed in the iMil group (data not shown). However, changes over time were observed in the control group for RVEDA ($p = 0.0363$), RADt ($p < 0.0001$) and TAPSE ($p = 0.0167$).

Between Groups Comparison

Between groups comparisons are depicted in Table 3 where only variables with significant differences are presented.

Hemodynamic Measurements: Groups were similar at T2 for all variables. However at T3, the means of the iMil group were higher for PCWP ($p = 0.0182$) and DPAP ($p = 0.0479$) and lower for PVR/SVR ($p = 0.0043$) as compared to the placebo group, but all of these differences vanished at T4. The only significant result at T4 was for CO, which had a lower mean in the iMil group ($p = 0.0445$).

Echocardiographic Measurements: As depicted in 3, the RVEDA and RVESA were different between groups. While the RVEDA mean was lower in the iMil group at T4 ($p = 0.0023$), the RVESA mean was higher in the iMil group at T2 ($p = 0.0361$). Also at T2, the means of the iMil group were higher for RADt ($p = 0.0367$) and lower for RVFAC ($p = 0.0366$). Finally, the only significant result at T3 was for LVESA with a higher mean in the iMil group ($p = 0.0106$).

The outcome and safety data are presented in Table 4. Because of the small number of patients, no statistical analysis was performed.

Variables*	Group	T1 (Baseline)	T2 (End Nebulization)	T3 (20 minutes)	T4 (After CPB)	*P* value
HR (beats/min)	Control	70.2 ± 4.4	67.5 ± 4.0	64.6 ± 3.1	77.3 ± 3.6	0.1035
	Inhaled Milrinone	63.9 ± 3.6	59.3 ± 3.6	65.6 ± 4.3	72.1 ± 2.4	0.0174[1]
SAP (mmHg)	Control	109.1 ± 7.5	109.8 ± 5.7	106.2 ± 2.2	111.3 ± 4.8	0.8375
	Inhaled Milrinone	114.3 ± 3.7	105.5 ± 9.0	106.2 ± 5.8	105.4 ± 5.6	0.2976
MAP (mmHg)	Control	73.4 ± 4.1	74.2 ± 3.4	71.9 ± 3.4	71.9 ± 2.8	0.9478
	Inhaled Milrinone	78.7 ± 4.3	75.2 ± 3.9	71.6 ± 4.0	72.4 ± 3.9	0.3781
CVP (mm Hg)	Control	10.1 ± 0.7	11.0 ± 1.2	10.9 ± 1.2	14.2 ± 2.0	0.0157[2]
	Inhaled Milrinone	12.7 ± 1.4	11.3 ± 1.6	13.0 ± 1.6	14.7 ± 1.6	0.2757
PCWP (mmHg)	Control	21.9 ± 1.6	20.3 ± 1.3	15.8 ± 1.7	21.5 ± 2.0	0.0632
	Inhaled Milrinone	24.2 ± 3.0	24.1 ± 2.1	23.5 ± 2.2	24.1 ± 2.8	0.8942
SPAP (mmHg)	Control	37.2 ± 3.6	39.4 ± 2.9	36.5 ± 3.0	39.3 ± 4.9	0.0147[3]
	Inhaled Milrinone	54.6 ± 7.0	49.6 ± 4.8	50.2 ± 7.8	47.0 ± 4.2	0.1338
DPAP (mmHg)	Control	20.7 ± 1.8	21.7 ± 1.6	19.5 ± 1.3	22.0 ± 2.5	0.0207[4]
	Inhaled Milrinone	26.2 ± 1.9	24.9 ± 1.7	26.0 ± 2.4	28.6 ± 4.7	0.5694
MPAP (mmHg)	Control	27.7 ± 2.5	29.3 ± 2.1	27.8 ± 2.3	29.1 ± 3.4	0.3788
	Inhaled Milrinone	38.1 ± 3.9	34.7 ± 3.0	36.1 ± 4.5	33.9 ± 2.3	0.1655
CO (L/min)	Control	3.1 ± 0.3	3.3 ± 0.3	3.0 ± 0.3	4.6 ± 0.3	<0.0001[5]
	Inhaled Milrinone	3.5 ± 0.3	3.5 ± 0.3	3.7 ± 0.3	3.8 ± 0.1	0.1150
SVR (dynes.sec.cm^{-5})	Control	1737.7 ± 170.9	1733.1 ± 181.3	1836.3 ± 249.6	1064.1 ± 80.0	0.0542
	Inhaled Milrinone	1647.5 ± 176.5	1541.4 ± 181.7	1347.8 ± 134.7	1106.4 ± 80.8	0.0465[6]
PVR (dynes.sec.cm^{-5})	Control	149.4 ± 26.7	216.9 ± 30.7	295.3 ± 41.7	134.0 ± 35.4	0.0376[7]
	Inhaled Milrinone	326.0 ± 35.0	265.1 ± 30.6	253.6 ± 45.5	164.8 ± 25.9	0.0458[8]
PVR/SVR (%)	Control	9.1 ± 1.3	12.9 ± 2.8	16.7 ± 2.2	11.6 ± 2.7	0.1292
	Inhaled Milrinone	20.7 ± 1.6	18.9 ± 3.1	20.9 ± 4.2	15.4 ± 2.4	0.2585

Table 2: Hemodynamic variables: one-way repeated ANOVA
*Variables expressed as adjusted mean ± standard error. T1: baseline after induction of anesthesia, T2: at the end of nebulization, T3: 20 minutes after nebulization before cardiopulmonary bypass (CPB), T4: during chest closure after CPB.
ANOVA, analysis of variance; HR, Heart rate; SAP, systemdic arterial pressure; MAP, mean arterial pressure; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; SPAP, systolic pulmonary arterial pressure; PAP, diastolic pulmonary arterial pressure; MPAP, mean pulmonary arterial pressure; CO, cardiac output; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance.
[1]HR increase in the milrinone group in T4 compared to T1 and T2 and in T3 compared withT2
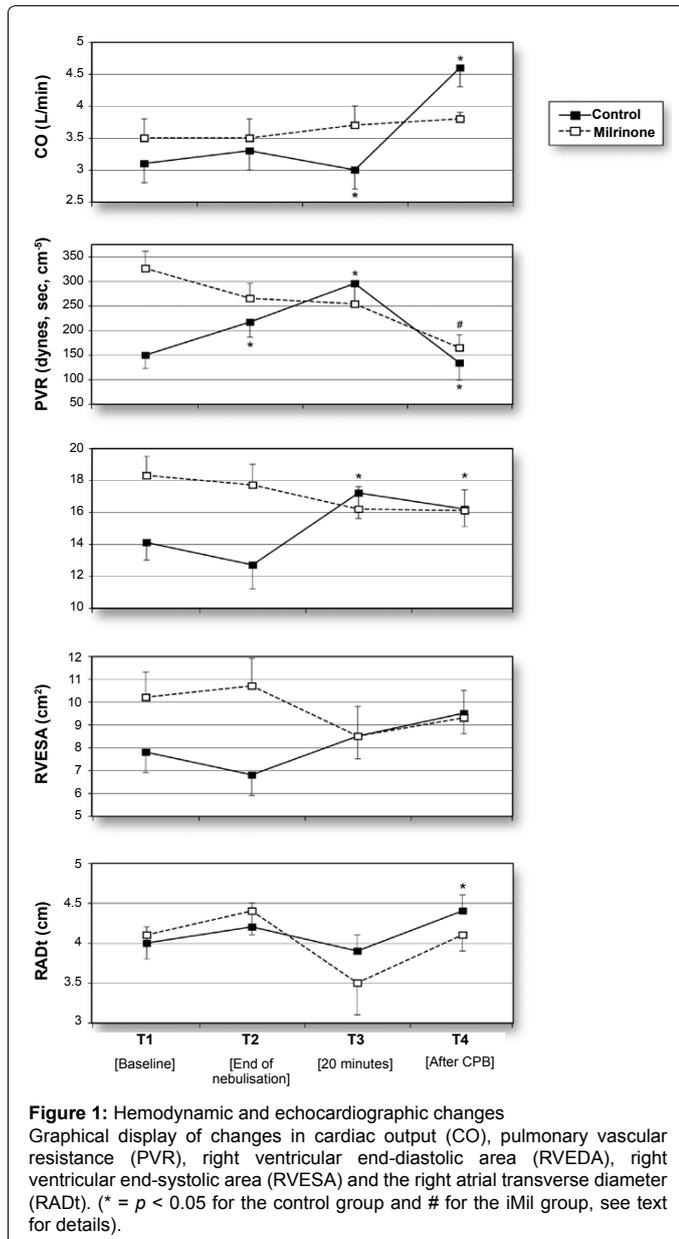[2]CVP in the control group became higher at T4 compared to T2
[3]SPAP in the control group lower at T3 compared to T2; [4]DPAP in the control group lower at T3 compared to T2
[5]CO in the control group lower at T3 compared to T2 and higher at T4 compared with T1,T2,T3
[6]SVR decrease in the milrinone group at T3 compared to T1 and T4 compared to T1 and T2
[7]PVR in the control group increase at T2 and T3 compared with T1 and decrease at T4 compared with T3
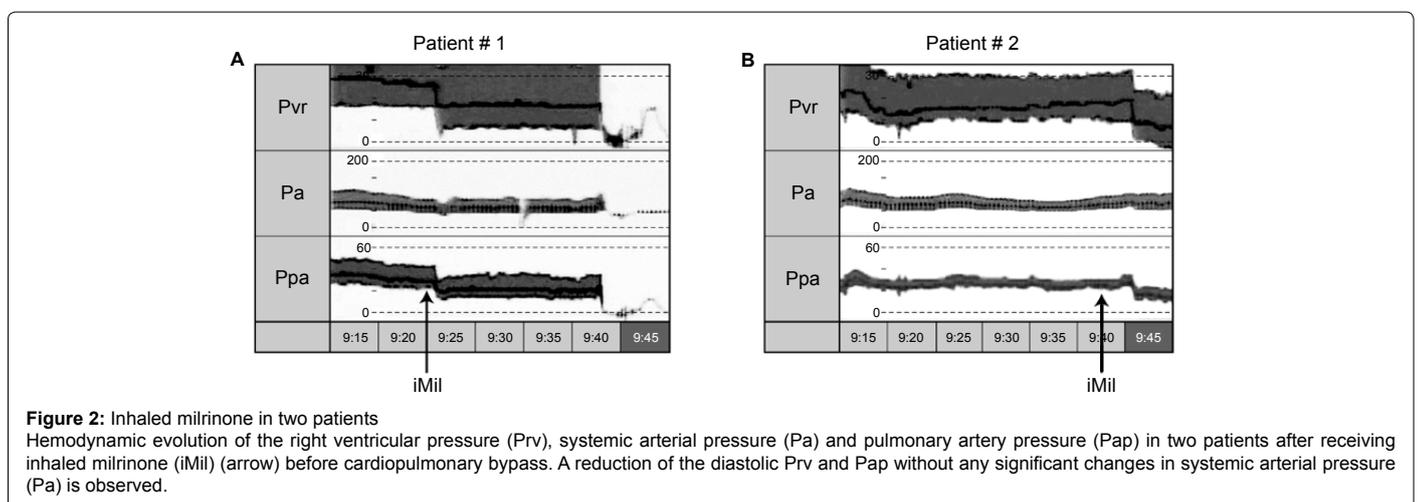[8]PVR in the milrinone group became lower at T4 compared to T2

Figure 1: Hemodynamic and echocardiographic changes
Graphical display of changes in cardiac output (CO), pulmonary vascular resistance (PVR), right ventricular end-diastolic area (RVEDA), right ventricular end-systolic area (RVESA) and the right atrial transverse diameter (RADt). (* = $p < 0.05$ for the control group and # for the iMil group, see text for details).

The iMil group required less intravenous milrinone (18% *vs.* 40%), no adrenaline after CPB and no intra-aortic balloon pump. One death occurred in the iMil group and two in the control group. The need for vasopressors for more than 24 hours, the prevalence of atrial fibrillation, ICU and hospital stay durations were similar. An example of the effect of milrinone on two patients is illustrated in Figure 2.

Discussion

This is the first randomized controlled double-blind trial on the use and safety of iMil in cardiac surgery in which both simultaneous hemodynamic and echocardiographic measurements were obtained. The administration of iMil in this high-risk population was not associated with any significant systemic hypotension compared to the control group. Furthermore, compared with a control group, we observed in the iMil group a modest reduction in the hemodynamic severity of pulmonary hypertension with unaltered ventricular dimensions consistent with a reduction or prevention of the increase in RV afterload. These hemodynamic effects of iMil are consistent with previous observations in animal [10,11] and human studies [16,17,28].

In our patients, before induction and at baseline, the iMil group had much more severe pulmonary hypertension with associated increased right-sided dimensions. Despite this unfavorable condition, no significant systemic hypotension was observed; only 2 patients (18%) required inotropes, and none returned on CPB or needed IABP to be weaned from CPB. Furthermore, reduction in right-sided chambers with reciprocal increase in LV dimensions appeared in the iMil group when compared to the control group. These changes could be explained by a reduction in RV afterload by iMil, leading to an increase in pulmonary flow. This would explain the maintenance of LV filling pressure (higher PCWP and DPAP) at 20 minutes after nebulization.

Milrinone is a cyclic AMP-specific phosphodiestersase inhibitor that can exert both positive inotropic effects and vasodilation independently of β_1-adrenergic receptor stimulation in the cardiovascular system [23,32]. Previous studies evaluating the use of intravenous milrinone in cardiac surgical patients were underpowered and performed on a small number of patients undergoing coronary revascularization [33]. Although milrinone has been shown to increase CO (34-36) and to facilitate separation from CPB [37], the major problem encountered with intravenous milrinone is the high incidence of systemic hypotension resulting in an increased need for vasoactive drugs [3,35,38,39]. The hypotension resulting from intravenous milrinone is either caused by vasodilation or through dynamic left or right ventricular outflow

Figure 2: Inhaled milrinone in two patients
Hemodynamic evolution of the right ventricular pressure (Prv), systemic arterial pressure (Pa) and pulmonary artery pressure (Pap) in two patients after receiving inhaled milrinone (iMil) (arrow) before cardiopulmonary bypass. A reduction of the diastolic Prv and Pap without any significant changes in systemic arterial pressure (Pa) is observed.

Variables*	Group	T2 (End Nebulization)	P value	T3 (20 minutes)	P value	T4 (After CPB)	P value
Hemodynamic							
PCWP (mmHg)	Control	20.5 ± 1.5	0.2539	16.6 ± 1.8	0.0182	22.3 ± 1.7	0.6198
	Inhaled milrinone	22.8 ± 1.3		22.7 ± 1.3		23.5 ± 1.6	
DPAP	Control	24 ± 1.0	0.4636	21 ± 0.9	0.0479[1]	26.7 ± 3.0	0.8447
	Inhaled milrinone	23.0 ± 0.97		23 ± 1.3		25.8 ± 3.0	
CO (L/min)	Control	3.5 ± 0.1	0.3198	3.1 ± 0.2	0.1992	4.6 ± 0.2	0.0445
	Inhaled milrinone	3.3 ± 0.1		3.5 ± 0.2		3.9 ± 0.2	
PVR/SVR (%)	Control	21 ± 4.4	0.3543	13.8 ± 5.2	0.0043[2]	8.3 ± 4.1	0.1953
	Inhaled milrinone	14.4 ± 3.7		8.3 ± 3.5		17.3 ± 3.7	
Echocardio-graphic							
RVEDA 4ch (cm²)	Control	14.0 ± 1.2	0.4759	19.1 ± 1.1	0.061	17.3 ± 0.7	0.0023
	Inhaled milrinone	15.4 ± 1.3		14.9 ± 1.5		12.7 ± 0.9	
RVESA 4ch (cm²)	Control	6.7 ± 0.8	0.0361	9.6 ± 0.9	0.2917	9.8 ± 0.8	0.0535
	Inhaled milrinone	10.1 ± 1.1		7.9 ± 1.2		7.3 ± 0.9	
RADt (cm)	Control	4.2 ± 0.2	0.0367[3]	4.1 ± 0.1	0.0905	4.3 ± 0.2	0.2129
	Inhaled milrinone	4.4 ± 0.2		3.5 ± 0.2		3.8 ± 0.3	
LVESA_sax (cm²)	Control	14 ± 0.7	0.5223	11.9 ± 0.29	0.0106[5]	13.3 ± 1.2	0.6105
	Inhaled milrinone	15 ± 1.2		14.1 ± 0.4		12.1 ± 1.9	
RVFAC (%)	Control	50.7 ± 3.1	0.0366[4]	49.5 ± 4	0.9662	41.7 ± 3.9	0.5458
	Inhaled milrinone	39 ± 2.9		49.2 ± 5.6		45.5 ± 4.7	

Table 3: One-way ANCOVA adjusted for T1 at separate time interval
*Variables expressed as adjusted mean ± standard error. Only significant variables are presented. T1: baseline after induction of anesthesia, T2: at the end of nebulization, T3: 20 minutes after nebulization before cardiopulmonary bypass (CPB), T4: during chest closure after CPB. ANCOVA, analysis of covariance; PCWP, pulmonary capillary wedge pressure; DPAP, diastolic pulmonary arterial pressure; CO, cardiac output; PVR/SVR, pulmonary to systemic vascular resistance ratio; RVEDA, right ventricular end-diastolic area; RVESA, right ventricular end-systolic area; RADt, right atrial transverse diameter; LVESA_sax, left ventricular short axis view from a mid-papillary transgastric view; RVFAC, right ventricular fractional area.
[1] DPAP had a tendency to be higher at T3 ($p = 0.0639$) in the upper quartile group of the inhaled milrinone group
[2] PVR/SVR ratio was higher in the control group in the lower quartile ($p = 0.0043$);
[3] RADt: Control group was smaller at T2 in the lower quartile ($p = 0.0437$)
[4] RVFAC was higher in the control group in the lower ($p = 0.0056$) and middle quartile ($p = 0.0182$)
[5] LVESA_sax was lower in the control group for the middle ($p = 0.0373$) and higher quartile ($p = 0.0130$)

	Control (n = 10)	Inhaled Milrinone (n = 11)
Difficult separation from CPB	7 (70%)	7 (64%)
Intravenous milrinone post-CPB	4 (40%)	2 (18%)
Intravenous adrenaline post-CPB	1 (10%)	0
Intra-aortic balloon pump requirement	1 (10%)	0
Vasopressors use > 24 hours	4 (40%)	5 (45%)
Atrial fibrillation	5 (50%)	6 (55%)
Death	2 (20%)	1 (9%)
ICU stay (hours)	45 (27-96)	72 (45-120)
Hospital stay (days)	6 (5-13)	13 (6-23)

Variables expressed as number (%) or as mean with 1st and 3rd interquartile range. CPB, cardiopulmonary bypass; ICU, intensive care unit.

Table 4: Outcome data.

tract obstruction [40]. Two randomized controlled trials on the use of milrinone in a non-cardiac surgical setting showed no advantage in terms of hospitalization duration [7,41]. Furthermore, patients receiving milrinone had more adverse events and higher mortality in the PROMISE trial [41]. So far, randomized controlled trials in cardiac surgery have not been designed, or sufficiently powered, to correlate mortality with intravenous milrinone, but the same issue could be encountered. Therefore, it appears relevant to explore alternative strategies such as iMil, which could reduce the severity of pulmonary hypertension without causing systemic hypotension. However, the first step was to document the absence of significant systemic hypotension in patients receiving iMil.

So far 229 patients have been reported being exposed to iMil in small unblinded trials [16,17,19,21,22,25], retrospective analysis [18] and case reports [23,24,26,42,43]. The effect of iMil was first described by Haraldsson *et al.* [16] in an open-label trial of 20 cardiac surgical patients in the intensive care unit. The first part of the trial included 9 patients and showed a dose-response effect of incremental concentrations of iMil with decreases in MPAP, PVR and PVR/SVR. No patient presented systemic hypotension. The hemodynamic parameters of patients treated with iMil returned to baseline within 20 minutes of the end of the inhalation period, similar to our observation. In the second study [17], iMil was given to 18 heart transplant candidates in the intensive care unit. The MPAP, transpulmonary gradient and PVR decreased only in patients with pulmonary hypertension, defined as MPAP above 30 mmHg. Improvement in CO was observed, but there was no systemic hypotension. The dosage was 2 mg based on intravenous milrinone loading doses used in heart transplantation, which was almost half of the dose used in our protocol. In these studies, there was no control group, and the intraoperative usage and the timing of iMil in relation to CPB were not recorded. We have previously described the administration of iMil before CPB in 40 high-risk patients with a Parsonnet score of 30.4 ± 14.2 [28]. Compared

to the administration of iMil after CPB, pre-CPB iMil was associated with a reduction of difficult separation from CPB (18% *vs*. 82%) defined as the use of more than two inotropes, need for introduction of an intra-aortic balloon pump or reinitiation of CPB. Finally a recent study compared the use of intravenous versus inhaled milrinone in 48 patients with pulmonary hypertension after mitral valve surgery [19]. With milrinone administration, mean pulmonary artery pressure and pulmonary vascular resistance decreased in both groups. However, the mean arterial pressure and systemic vascular resistance in the inhaled group were significantly higher than in the intravenous group. In addition, in the inhaled group, there was a reduction in intrapulmonary shunt fraction in the inhaled milrinone group.

In the current study, the same ratio was observed; 4 patients in the control group compared to 1 in the iMil group would have qualified for this definition. Significantly lower SPAP and unchanged LV function were also observed after CPB in the group who received iMil pre-CPB, as observed in the current study, but RV function was not analyzed. Finally a recent study compared the use of intravenous versus inhaled milrinone in 48 patients with pulmonary hypertension after mitral valve surgery [19] . With milrinone administration, mean pulmonary artery pressure and pulmonary vascular resistance decreased in both groups. However, the mean arterial pressure and systemic vascular resistance in the inhaled group were significantly higher than in the intravenous group. In addition, in the inhaled group, there was a reduction in intrapulmonary shunt fraction in the inhaled milrinone group.

Administration of iMil before CPB could be advantageous for several reasons. First, iMil could protect the pulmonary vasculature during weaning from CPB when ischemia-reperfusion injury occurs through a more uniform distribution and penetration in mechanically ventilated lungs free of significant post-CPB atelectasis [10]. This may explain why patients receiving iMil before CPB were found to have lower or similar MPAP after separation from CPB [28]. These findings were not observed when intravenous milrinone [10] was administered or when the administration of the drug occurred after CPB [28]. Secondly, the administration of iMil before CPB could prevent the reperfusion syndrome [44].

Limitations

There are several study limitations that need to be addressed. The number of patients is small. It was important for us to determine the safety of iMil given intraoperatively in patients under general anesthesia because it had not been studied in this context previously. Before the induction and at baseline before drug administration, the iMil patients had more severe pulmonary hypertension. Therefore, after presenting the observed values and performing the same analysis as originally published by Haraldsson and Sablotzki [16,17], we compared both groups using two-way ANCOVA with adjusted values. Despite the small number of patients, we observed differences in PVR/SVR and RV dimensions between the groups consistent with a RV afterload effect of iMil. The absolute effect of iMil on the severity of pulmonary hypertension was modest but similar to that described in previous observational studies [16,17]. The number of patients was too small to explore other significant outcomes such as length of intensive care unit stay, hospitalization duration and mortality. However, this study was the necessary step to confirm our animal and preliminary human observations and the safety of this new strategy. Finally, systemic exposition to milrinone was not documented in these patients. We have previously reported that milrinone concentration obtained in cardiac patients having the same characteristics are below 30 ng/mL when milrinone is given by inhalation [45].Milrinone levels below 100 ng/

mL are not likely to induce significant systemic hypotension in cardiac patients [46].

Conclusion

In summary, the administration of iMil before initiation of CPB is not associated with any significant systemic hypotension. In patients receiving iMil, we observed a mild reduction in the severity of pulmonary hypertension with improved right-sided cavity dimensions compared to the control group. Further studies with larger numbers of patients are required to document the potential benefit of this approach in the care of cardiac surgical patients with pulmonary hypertension.

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