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REPORTS OF ORIGINAL INVESTIGATIONS

A multicentre randomized-controlled trial of inhaled milrinone in high-risk cardiac surgical patients

Une étude randomisée contrôlée multicentrique sur la milrinone inhalée chez les patients de chirurgie cardiaque à risque élevé

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Abstract

Purpose *Inhaled milrinone (iMil) has been used for the treatment of pulmonary hypertension (PH) but its efficacy, safety, and prophylactic effects in facilitating separation from cardiopulmonary bypass (CPB) and preventing right ventricular (RV) dysfunction have not yet been evaluated in a clinical trial. The purpose of this study was to investigate if iMil administered before CPB would be superior to placebo in facilitating separation from CPB.*

Methods *High-risk cardiac surgical patients with PH were randomized to receive iMil or placebo after the induction of anesthesia and before CPB. Hemodynamic parameters and RV function were evaluated by means of pulmonary artery catheterization and transesophageal echocardiography. The groups were compared for the primary outcome of the level of difficulty in weaning from CPB. Among the secondary outcomes examined were the reduction in the severity of PH, the incidence of RV failure, and mortality.*

Results *Of the 124 patients randomized, the mean (standard deviation [SD]) EuroSCORE II was 8.0 (2.6), and the baseline mean (SD) systolic pulmonary artery pressure (SPAP) was 53 (9) mmHg. The use of iMil was associated with increases in cardiac output (P = 0.03) and*

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a reduction in SPAP (P = 0.04) with no systemic hypotension. Nevertheless, there was no difference in the combined incidence of difficult or complex separation from CPB between the iMil and control groups (30% vs 28%, respectively; absolute difference, 2%; 95% confidence interval [CI], −14 to 18; P = 0.78). There was also no difference in RV failure between the iMil and control groups (15% vs 14%, respectively; difference, 1%; 95% CI, −13 to 12; P = 0.94). Mortality was increased in patients with RV failure vs those without (22% vs 2%, respectively; P < 0.001).

Conclusion *In high-risk cardiac surgery patients with PH, the prophylactic use of iMil was associated with favourable hemodynamic effects that did not translate into improvement of clinically relevant endpoints. This trial was registered at ClinicalTrials.gov; identifier: NCT00819377.*

Résumé

Objectif *La milrinone inhalée est utilisée pour traiter l'hypertension pulmonaire (HP) mais son efficacité, son innocuité et ses effets prophylactiques pour faciliter le sevrage de la circulation extracorporelle (CEC) et prévenir la dysfonction ventriculaire droite (VD) n'ont pas encore été évalués dans le cadre d'une étude clinique. L'objectif de cette étude était d'examiner si la milrinone inhalée avant la CEC serait supérieure à un placebo pour faciliter le sevrage de la CEC.*

Méthode *Des patients de chirurgie cardiaque à risque élevé et souffrant d'HP ont été randomisés à recevoir de la milrinone inhalée ou un placebo après l'induction de l'anesthésie et avant la CEC. Les paramètres hémodynamiques et la fonction VD ont été évalués à l'aide d'un cathéter de l'artère pulmonaire et d'une échocardiographie transœsophagienne. Les groupes ont été comparés selon notre critère d'évaluation principal, soit le niveau de difficulté du sevrage de la CEC. Parmi les critères d'évaluation secondaires examinés figuraient la réduction de la gravité de l'HP, l'incidence d'insuffisance cardiaque droite et la mortalité.*

Résultats *Au total, 124 patients ont été randomisés. Le score EuroSCORE II moyen (écart type [ÉT]) était de 8,0 (2,6), et la pression systolique de l'artère pulmonaire moyenne de base (ÉT) était de 53 (9) mmHg. L'utilisation de milrinone inhalée a été associée à des augmentations du débit cardiaque (P = 0,03) et à une réduction de la pression systolique de l'artère pulmonaire (P = 0,04) sans hypotension systémique. Toutefois, aucune différence n'a été observée dans l'incidence combinée de sevrage difficile ou complexe de la CEC entre le groupe milrinone inhalée et le groupe témoin (30 % vs 28 %, respectivement; différence absolue, 2 %; intervalle de confiance [IC] 95 %, −14 à 18; P = 0,78). Aucune différence n'a été observée non plus en matière d'insuffisance cardiaque droite entre le groupe milrinone inhalée et le groupe témoin (15 % vs 14 %, respectivement; différence, 1 %; IC 95 %, −13 à 12; P = 0,94). La mortalité était augmentée chez les patients avec insuffisance cardiaque droite (22 % vs 2 %, respectivement; P < 0.001).*

Conclusion *Chez les patients de chirurgie cardiaque à risque élevé atteints de HP, l'utilisation prophylactique de milrinone inhalée a été associée à des effets hémodynamiques favorables qui ne se sont pas traduits en améliorations des critères pertinents d'un point de vue clinique. Cette étude a été enregistrée au ClinicalTrials.gov; identifiant : NCT00819377.*

Pulmonary hypertension (PH) is a major cause of mortality and morbidity in patients undergoing cardiac surgery.[1] Studies have suggested that intravenous milrinone may be beneficial in the treatment of PH in cardiac surgery.[2,3] Nevertheless, intravenous milrinone has been associated with systemic hypotension[4] and increased vasoactive drug requirements[5] as well as increased morbidity[6] and mortality after cardiac surgery.[7]

The use of inhaled milrinone (iMil) has been described in several animal[8,9] and human reports.[10-26] Compared with its alternatives [i.e., inhaled nitric oxide (iNO) and inhaled prostacyclin ($iPGI_2$)], iMil possesses inotropic properties, is less expensive, does not require a complex administration system, and does not have toxic metabolites. Furthermore, contrasted with $iPGI_2$, iMil is readily available in most cardiac operating rooms and needs no special preparation. In addition, iMil administered before cardiopulmonary bypass (CPB) has been shown to be superior to its intravenous form in reducing pulmonary reperfusion syndrome that has been associated with endothelial dysfunction.[9,27]

Although iMil has been proposed as a treatment for PH and right ventricular (RV) failure,[20,25] at present, there is a lack of large studies comparing it with placebo in a double-blind fashion. Accordingly, the primary purpose of this study was to compare iMil administered before CPB with placebo to determine its impact on facilitating separation from CPB. Our main hypothesis was that the administration of iMil before CPB would be superior to placebo in reducing the difficulty in separation from CPB. Other endpoints examined were related to its safety and efficacy in reducing the severity of PH and the incidence of RV dysfunction.

Methods

Study design

This prospective randomized double-blind placebo-controlled phase III study was conducted in four

Canadian University Medical Centres from April 2009 to November 2011 (with patient follow-up until January 2014). The study was conducted in compliance with the Declaration of Helsinki, the "Énoncé de politiques des trois Conseils II" and its amendments, and the International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use and Good Clinical Practice guidelines. The study protocol was approved by the appropriate Ethics Committees/ Institutional Review Boards (ICM-081004 approved in October 2008) and Health Canada (#118983). Written informed consent was obtained from all patients.

Patients

Patients ($n = 140$) $\geq$ 18 yr were eligible for inclusion in the study if they were scheduled for an elective valvular operation or complex (defined as either two or more valves or valve and coronary artery bypass grafting) cardiac surgery with CPB and were diagnosed with preoperative PH. Pulmonary hypertension was defined as a mean pulmonary artery pressure (MPAP) $>$ 30 mmHg or a systolic pulmonary artery pressure (SPAP) $>$ 40 mmHg, measured during preoperative right-sided catheterization or estimated by using Doppler echocardiography. Patients were excluded if they had surgery without CPB, preoperative hemodynamic instability (defined as acute requirement for vasoactive support or mechanical device), congenital heart disease, a contraindication to transesophageal echocardiography (TEE), or were having emergency surgery.

Anesthesia protocol

Premedication was administered according to local practices. Routine monitoring[28] included a five-lead electrocardiogram, pulse oximeter, invasive blood pressure (radial artery cannulation), in addition to placement of a thermodilution pulmonary artery catheter (Swan-Ganz catheter 7.5F; Baxter Healthcare Corporation, Irvine, CA, USA). Anesthesia was induced with midazolam 0.04 $mg \cdot kg^{-1}$ and sufentanil 1 $\mu g \cdot kg^{-1}$, and muscle relaxation was achieved with pancuronium 0.1 $mg \cdot kg^{-1}$ or rocuronium 1 $mg \cdot kg^{-1}$. After tracheal intubation, anesthesia was maintained throughout the procedure with sufentanil 1 $\mu g \cdot kg^{-1} \cdot hr^{-1}$, midazolam 0.04 $mg \cdot kg^{-1} \cdot hr^{-1}$, and isoflurane or sevoflurane according to local practice. No volatile anesthetic gases were used for induction. Minute ventilation was adjusted to maintain end-tidal carbon dioxide in the range of 30-40 mmHg.

Pharmacological treatment

The day before surgery, eligible patients were randomized (1:1) in a double-blind manner to receive either a single dose of iMil (Primacor; Sanofi-Synthelabo Canada Inc., Markham, ON, Canada) or placebo (equal volume 0.9% saline). Central randomization was employed using a computer-assisted method with SAS® Proc Plan (SAS version 9.2; SAS Institute Inc., Cary, NC, USA). Research assistants conducted the recruitment and allocation sequence, and a research pharmacist not involved in the trial performed the drug or placebo preparation. The study drug or placebo was administered after induction of anesthesia once the baseline hemodynamic profiles and TEE exam were completed. Both agents were administered through an ultrasonic mesh nebulizer (Aeroneb® Professional Nebulizer System; Aerogen Ltd., Galway, Ireland) attached to the inspiratory branch of the respiratory limb of the ventilator near the endotracheal tube, with filters on the expiratory limb, as previously described.[17] The iMil and placebo were identical in appearance. The 5-mg dose selected (resulting in a range of 50-80 $\mu g \cdot kg^{-1}$) was based on previous studies, our experience in using iMil,[10,11,14,17] and various pharmacokinetic (PK) studies.[22,29,30] Concomitant medications were permitted according to local standards of care, with the exception of iMil.

Intraoperative management

Intravenous fluids (0.9% normal saline) were administered according to estimated insensible losses of 7 $mL \cdot kg^{-1} \cdot hr^{-1}$ during the surgery and titrated according to blood pressure and central venous pressure (CVP). A decrease in mean arterial pressure (MAP) $<$ 60 mmHg was treated by fluid administration (in the presence of a low CVP) or by the use of vasopressors (noradrenaline or phenylephrine) according to a predetermined protocol, as previously described.[31,32] During CPB (CPB flow = 2.2 $L \cdot min^{-1} \cdot m^{-2}$), blood cardioplegia was used in all patients. Induction and maintenance of cardioplegia were cold to tepid (10-29°C). Venous temperature was allowed to drift to 34°C for coronary artery bypass procedures and was maintained at 32-34°C for valve and complex procedures and at 15-18°C for aortic procedures with circulatory arrest. Separation from CPB was attempted after temperature (central and bladder) was $>$ 36°C. The anesthesiologist had discretion to administer additional intravenous milrinone in the case of low cardiac output (CO) with reduced contractility documented using TEE. In the presence of post-CPB PH or RV failure (defined below), patient management included intravenous nitroglycerine and intravenous milrinone, and, in more

severe cases, iNO or $iPGI_2$. Nevertheless, administration of the two agents was not allowed before CPB. Patients were followed until discharge from the hospital, and they were then contacted by phone or at the valve clinic at 30 days, three months, and 12 months to evaluate survival.

Data collection

At the time of randomization, demographic, diagnostic (New York Heart Association Functional Classification, Parsonnet score, EuroSCORE II, comorbidities, left ventricular ejection fraction), and therapeutic (medication, type of surgery, reoperations) information was recorded. Heart rate (HR) and systemic blood pressure were obtained in the awake state before induction of anesthesia (time = T0). In order to confirm the presence of PH, hemodynamic values were obtained after induction of anesthesia and before nebulization (time = T1). Measurements were then performed 20 min after the start of nebulization and before the onset of CPB (time = T2). Measurements were repeated 20 min after separation from CPB (time = T3) and after sternal closure (time = T4). The measured hemodynamic parameters included HR, MAP, CVP, pulmonary artery occlusion pressure (PAOP), SPAP, MPAP, and diastolic pulmonary artery pressure (DPAP). The CO was assessed using the thermodilution technique with three injections of room temperature 5% dextrose 10 mL, and PAOP was measured at end expiration.

All TEE exams were performed by experienced anesthesiologists and reviewed offline by a cardiologist blinded to the allocation group. The intraclass and interclass correlation coefficients of variation of all echocardiographic measurements using ten random patients are shown in Table A (available as Electronic Supplementary Material). The examination included a mid-esophageal four-chamber view, a short-axis transgastric view at the mid-papillary level, and colour flow Doppler imaging of all the valves to detect any significant valvular disease. The RV function was evaluated using the four-chamber view with standard measurements, as previously described[33] and according to published guidelines.[34] The following measurements were obtained: right atrial transverse diameter (RADt), RV dimensions (at the annulus [RVD1], at the mid-portion [RVD2], and from the apex to the RV annular plane [RVD3]), the RV end-diastolic area (RVEDA), the RV end-systolic area (RVESA), the percentage of RV fractional area change (RVFAC) calculated as (RVEDA-RVESA)/RVEDA, and the tricuspid annular plane systolic excursion (TAPSE). Measurements were averaged over three consecutive cycles. Two-dimensional images were excluded if the endocardial border could not be traced adequately using Schnittger's criterion.

Outcome measures

The primary outcome was the number of patients classified as having difficult or complex separation from CPB. Weaning from CPB was graded as difficult (or pharmacological) when at least two different types of pharmacological agents (i.e., inotropes and vasopressors) were required. Weaning was graded as complex (or surgical) if both pharmacological support and a surgical intervention [e.g., return on CPB or the addition of a mechanical support system, such as an intra-aortic balloon pump (IABP)] were needed or if intraoperative death from heart failure occurred.[35,36]

The definition[36] for the secondary endpoint of RV failure was based on the presence of all three of the following: 1) hemodynamic instability, defined as difficult or complex separation from CPB; 2) > 20% reduction in RV fraction area measured by two-dimensional echocardiography; and 3) anatomical visualization of impaired or absent RV wall motion by direct intraoperative visual inspection. Additional secondary endpoints included the need for rescue therapy for postoperative PH, intraoperative persistent arrhythmias requiring medical intervention, cardioversion of defibrillation, the need for vasoactive support for more than 24 hr, duration of intubation, length of intensive care unit (ICU) and hospital stay, intraoperative mortality, and mortality up to one year. The endpoints were determined by the cardiac anesthesiologists who were blinded to the assignment group.

Pharmacokinetic and pharmacodynamic (PD) substudy

This substudy involved 45 patients from one (Montreal Heart Institute) of the five sites. In order to determine milrinone blood concentrations, six arterial blood samples were collected into heparinized tubes from patients having received either milrinone (n = 22) or saline (n = 23). Samples were drawn before drug administration (0 min) and at approximately ten, 15, 20, 25, and 30 min after the start of milrinone or saline nebulization. Samples were kept in an ice-water bath until centrifugation (15 min at 1,900 g). The plasma supernatant was frozen at −70°C until high-performance liquid chromatography-tandem mass spectrometry analysis.[29,30] Hemodynamic parameters (MAP and MPAP) were recorded at times corresponding to blood collection, and the MAP/MPAP ratio was calculated as a pharmacodynamic marker.[37,38] Non-compartmental analysis was subsequently performed on PK and PD data using Phoenix™ software (Certara, St. Louis, MO, USA). The non-compartmental analysis was performed using plasma and drug effect models with uniform weighting and intravenous infusion dosing. Peak

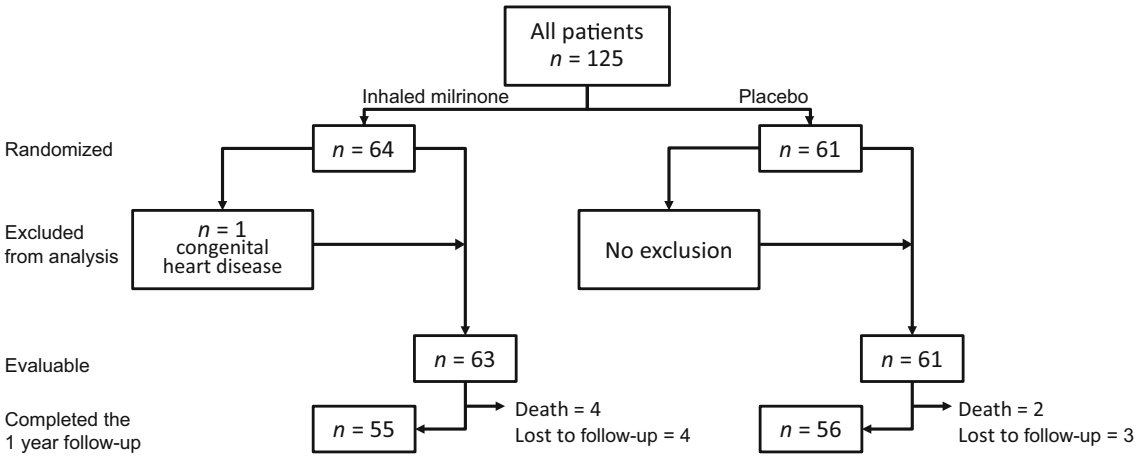

Fig. 1 CONSORT diagram showing the disposition of patients

concentrations (Cmax) and their corresponding times (Tmax) were determined. To calculate areas under the curve (AUC), a linear-linear trapezoidal method was used for both PK and PD data beginning at the start of nebulization until the time point corresponding to maximum concentration ($AUC_{0\text{-}Tmax}$). For PD data AUC calculation, both positive and negative fluctuations from the predetermined baseline response (R0; reference value) were taken into account during integration, yielding a net AUC. The relationship between the AUC and the corresponding individual AUCs was then investigated.

Statistical analysis

Based on our previous study,[17] we expected that the proportion of difficult and complex weaning from CPB would be 30% in the placebo group and 10% in the iMil group. Accordingly, a sample size of 124 patients (62 in each group) would have a power of 0.8 to detect a 20% absolute reduction in difficult and complex weaning from CPB between the inhaled placebo and iMil groups with an alpha of 0.05 (nQuery Advisor® version 4.0; Statistical Solutions Ltd., Cork, Ireland). Descriptive statistics for continuous variables are presented as mean (SD) or median [interquartile range (IQR)] according to the normality of distribution for the variable, which was verified using the Shapiro-Wilk test. Categorical variables are presented as frequency (percentage). The comparison of the two randomized groups in terms of outcomes (including the primary endpoint, separation from CPB, and the main secondary endpoint, RV failure) was done using Student's *t* test or the Mann-Whitney U-test for continuous variables and χ^2 test for categorical variables. The main analyses of the primary and secondary efficacy endpoints were conducted according to an intention-to-treat principle. Logistic regressions were used to determine potential predictors of difficult and complex separation from CPB and RV failure. In order to correct for the variable duration of each patient's procedure, the hemodynamic and echocardiographic measurements from T2 to T4 were analyzed over time by making use of linear mixed models to characterize individual trajectories. Baseline values at T1 were controlled, and values at T2 to T4 were used as dependent variables. Statistical analyses were performed using SAS® version 9.2 or higher (SAS Institute Inc., Cary, NC, USA). All reported *P* values are two sided.

Results

Of the 140 patients who consented to participate, 15 patients were excluded before surgery for various reasons, including preoperative hemodynamic instability ($n = 6$), schedule change for emergencies ($n = 2$), lacking availability of an intraoperative echocardiographer ($n = 3$), technical problems with nebulizers ($n = 1$), inclusion in another study ($n = 1$), no PH after induction of anesthesia ($n = 1$), and an unexpected finding of a large thrombus in the left atrium ($n = 1$) which was thought to contribute to PH. Furthermore, one patient in the treatment group was excluded because of previous congenital heart disease. Hence, 124 patients (iMil, $n = 63$; placebo, $n = 61$) completed the study (Fig. 1).

The control and iMil groups appeared to be well matched with respect to the mean (SD) Parsonnet score [29 (8) *vs* 31 (10), respectively], the mean (SD) EuroSCORE II [8 (3) *vs* 8 (23), respectively], pulmonary artery pressures, age, demographics, comorbidities, surgical procedures, medications, and laboratory data (Table 1). Nevertheless, there was a numerically higher percentage of males *vs* females in the control group (57% *vs* 40%, respectively) with higher body weight and body

Table 1 Baseline characteristics of the study population

Characteristics	Control (n=61)	Inhaled milrinone (n=63)
Age (yr)	68.3 (9.2)	70.2 (10.2)
Sex (male)	35 (57%)	25 (40%)
Weight (kg)	81.9 (18.5)	72.8 (16.0)
Height (cm)	164.4 (10.0)	161.6 (9.1)
BMI ($kg \cdot m^{-2}$)	30.2 (5.9)	27.8 (4.9)
Parsonnet score	29.1 (7.7)	30.8 (9.7)
EuroSCORE II	7.7 (2.5)	8.3 (2.7)
Cardiac disease		
Prior myocardial infarction	11 (18%)	8 (13%)
Angina	19 (31%)	21 (33%)
Atrial fibrillation	24 (39%)	24 (38%)
Congestive heart failure	20 (33%)	19 (30%)
NYHA 1	1 (5%)	1 (5%)
NYHA 2	4 (20%)	4 (21%)
NYHA 3	12 (60%)	13 (68%)
NYHA 4	3 (15%)	1 (5%)
Valvular disease		
Mitral valvular disease	51 (84%)	53 (84%)
Stenosis	11 (22%)	13 (24%)
Regurgitation	40 (78%)	40 (75%)
Aortic valvular disease	43 (70%)	42 (67%)
Stenosis	25 (59%)	28 (70%)
Regurgitation*	17 (40%)	12 (30%)
Other valvular disease	30 (49%)	35 (56%)
Tricuspid valve regurgitation	30 (100%)	35 (100%)
Pulmonic valve regurgitation	2 (7%)	5 (14%)
Normal LVEF	45 (82%)	42 (76%)
Comorbidities		
Hypertension	46 (75%)	46 (73%)
Diabetes mellitus	13 (21%)	10 (16%)
Cerebrovascular disease	10 (16%)	8 (13%)
Peripheral vascular disease	10 (16%)	4 (6%)
Renal failure	7 (11%)	2 (3%)
COPD	10 (16%)	9 (14%)
Surgical procedures		
Mitral valvular surgery or repair	35 (57%)	37 (59%)
Aortic valve surgery or repair	37 (61%)	34 (54%)
Tricuspid valve surgery or repair	7 (11%)	10 (16%)
Previous cardiac surgery	10 (16%)	16 (25%)
Drug therapy at admission		
Heparin	10 (16%)	9 (14%)
Antiplatelets	38 (62%)	27 (43%)
Oral nitrates	10 (16%)	6 (10%)
Calcium channel antagonists	17 (28%)	17 (27%)
Beta-blockers	37 (61%)	37 (59%)
ACE inhibitors	18 (30%)	27 (43%)
ARA	12 (20%)	2 (3%)
Antiarrhythmic	4 (7%)	5 (8%)
Digoxin	4 (7%)	7 (11%)
Diuretics	41 (67%)	36 (57%)
Laboratory values		
Hemoglobin ($g \cdot L^{-1}$)	130.2 (17.3)	126.6 (21.2)
Creatinine ($mMol \cdot L^{-1}$)	97.8 (27.2)	90.9 (23.6)
CKMB ($\mu g \cdot L^{-1}$)	2.9 [1.9-13.5]	3.1 [2.2-3.5]
Troponin ($\mu g \cdot L^{-1}$)	0.01 [0.01-0.01]	0.01 [0.01-0.01]
Baseline preoperative pulmonary hemodynamic data		
SPAP (mmHg)	54.1 (10.1)	52.9 (8.8)
MPAP (mmHg)	37.4 (10.1)	34.0 (6.5)

* Combined aortic stenosis and regurgitation in 4 patients in the control and in 8 patients in the inhaled milrinone group. Values represent mean (SD), n (%), or median [interquartile range], as indicated

ACE = angiotensin-converting enzyme; ARA = angiotensin receptor antagonist; BMI = body mass index; CABG = coronary artery bypass graft; CKMB = creatine phosphokinase MB fraction; COPD = chronic obstructive pulmonary disease; CPB = cardiopulmonary bypass; LVEF = left ventricular ejection fraction; MPAP = mean pulmonary artery pressure; NYHA = New York Heart Association; SPAP = systolic pulmonary artery pressure

mass index. Also, the control group patients used more preoperative anti-platelet agents and angiotensin receptor antagonists. Mitral valvular disease was present in 84% of both groups, and aortic valvular disease was present in 70% of the control group and 67% of the iMil group. Details of the procedures can be found in Table B (available as Electronic Supplementary Material). Mean (SD) duration of CPB was similar between groups [123 (48) min *vs* 120 (48) min in the control and iMil groups, respectively].

Outcome

The outcome and safety data are presented in Tables 2, 3 and 4. There was no significant difference in the combined incidence of difficult or complex separation from CPB between the iMil and control groups (30% *vs* 28%, respectively; absolute difference, 2%; 95% confidence interval [CI], −14 to 18; $P = 0.78$) or any of the other secondary outcomes. Eighteen (14.5%) patients developed RV failure associated with increased mortality (22%, RV failure *vs* 2%, no RV failure; $P < 0.001$). Using logistic regression, the risk factors for RV failure were a higher

Table 2 Main outcomes

Characteristics	Control (*n*=61)	Inhaled milrinone (*n*=63)	Difference of % (95% CI)	*P* value
Separation from CPB				0.78
Easy	44 (72%)	44 (70%)		
Combined difficult and complex	17 (28%)	19 (30%)	2 (−14 to 18)	
Difficult (pharmacological)	11 (18%)	7 (11%)		
Complex (pharmacological and mechanical)	6 (10%)	12 (19%)		
Return to CPB	6 (10%)	12 (19%)	9 (−3 to 21)	0.15
IABP requirement	1 (2%)	0	−2 (−5 to 1)	0.31
Right ventricular failure	9 (15%)	9 (14%)	−5 (−13 to 12)	0.94

Values represent *n* (%). CI = confidence interval; CPB = cardiopulmonary bypass; IABP = intra-aortic balloon pump

Table 3 Intraoperative characteristics

	Control (*n*=61)	Inhaled milrinone (*n*=63)	*P* value
Cardiopulmonary bypass duration (min)	123 (48)	120 (48)	0.73
Cross-clamping duration (min)	95 (35)	94 (44)	0.45
Intravenous agents after CPB			
Noradrenaline	38 (62%)	33 (52%)	0.26
Adrenaline	17 (28%)	14 (22%)	0.47
Dobutamine	2 (3%)	3 (5%)	0.67
Milrinone	3 (5%)	2 (3%)	0.62
Phenylephrine	0 (0%)	3 (5%)	0.08
Vasopressin	4 (7%)	1 (2%)	0.16
Inotropes	21 (34%)	17 (27%)	0.37
None	40 (66%)	46 (73%)	
1	20 (33%)	15 (24%)	
2	1 (2%)	2 (3%)	
Vasopressors	38 (62%)	34 (54%)	0.35
None	23 (38%)	29 (46%)	
1	34 (56%)	31 (49%)	
2	4 (7%)	3 (5%)	
Postoperative pulmonary hypertension requiring rescue therapy	2 (3%) (iNO and $IPGI_2$)	4 (6%) (iNO and $IPGI_2$ in 3 patients)	0.43
Intraoperative dysrhythmias	29 (47%)	30 (48%)	0.99

Values represent mean (standard deviation) or *n* (%), as indicated

CPB = cardiopulmonary bypass; iNO = inhaled nitric oxide; $iPGI_2$ = inhaled prostacyclin

mean (SD) EuroSCORE II [9.6 (2.7) *vs* 7.7 (2.5), respectively; OR, 1.56; 95% CI, 1.16 to 2.08; $P = 0.003$] and higher mean (SD) baseline RV end-systolic area (RVRSA) [13.7 (5.8) *vs* 10.4 (4.2), respectively; OR 1.2; 95% CI, 1.07 to 1.42; $P = 0.004$].

Hemodynamic and echocardiographic results

The hemodynamic and echocardiographic results are shown in Tables 5 and 6. There were 58 (95%) and 61 (97%) echocardiographic measurements evaluated in the control and iMil groups, respectively using the Schnittger criteria.[39] When comparing changes from T1 (baseline) to T2 (end of nebulization), the administration of iMil was associated with an increase in only mean (SD) CO [from 3.1 (0.8) $L \cdot min^{-1}$ to 3.5 (1.2) $L \cdot min^{-1}$; $P = 0.03$] and mean (SD) stroke volume [from 54 (18) mL to 56 (22) mL; $P = 0.01$]. There were no changes in heart rate, no systemic hypotension, no reduction in the severity of PH indices, and no significant changes in echocardiographic measurements.

The significant hemodynamic and echocardiographic results of the linear mixed models analyses are presented in Fig. 2 and detailed in Table C (available as Electronic

Table 4 Postoperative intensive care unit characteristics

	Control (n=61)	Inhaled milrinone (n=63)	P value
Postoperative complications			
Re-intubation	3 (5%)	4 (6%)	0.73
Vasoactive agents after ICU admission < 24 hr (%)	17 (28%)	17 (27%)	0.91
Noradrenaline	8 (13%)	8 (13%)	0.94
Adrenaline	7 (12%)	9 (14%)	0.64
Dobutamine	1 (2%)	2 (3%)	0.58
Milrinone	8 (13%)	8 (13%)	0.94
Phenylephrine	1 (2%)	0	0.31
Vasopressin	5 (8%)	1 (2%)	0.09
Duration of intubation (hr)	6.8 [4.4-17]	8.5 [5.3-18.2)]	0.21
ICU stay (hr)	26.1 [21.7-70.8]	42.9 [21.4-75.5]	0.64
Hospital stay (days)	7 [5-10]	8 [6-11]	0.32
Mortality at one year	3 (5%)	3 (5%)	

Values represent n (%) or median [interquartile range], as indicated. ICU = intensive care unit

Supplementary Material). Predicted means for iMil and placebo were obtained by fixing baseline values (T1) at the means of all patients (SPAP = 39.9 mmHg; DPAP = 20.1 mmHg; PAOP = 19.0 mmHg; RADt = 4.28 cm). When controlling for baseline values at T1, iMil was found to reduce SPAP by 4.1 mmHg at the end of nebulization (T2) compared with the placebo group ($P = 0.04$). Nevertheless, this difference diminished over time ($P = 0.04$). The DPAP and PAOP showed similar results. When controlling for baseline values at T1, the DPAP and PAOP means were similar between the iMil and placebo groups at the end of nebulization (T2). Due to statistically significant interactions, however, means increased faster in the placebo group than in the iMil group ($P = 0.04$). Finally, RADt means were higher in the iMil group than in the placebo group at the end of nebulization (T2). Nevertheless, this difference decreased and reversed over time.

Pharmacokinetic and PD study

Pharmacokinetic and PD data were available for 19 and 18 patients, respectively, in the iMil subgroup. Examples of concentration- and effect-time profiles for two different patients are shown in Fig. 3. The mean (SD) Cmax and Tmax were 86.8 (8.8) $ng{\cdot}mL^{-1}$ and 20.5 (6.5) min, respectively. In the iMil subgroup, the mean (SD) AUC from time 0 (beginning of nebulization) to Tmax ($AUC_{0\text{-}Tmax}$) for plasma concentrations was 1,258 (559) $ng{\cdot}min{\cdot}mL^{-1}$. In the placebo subgroup, the mean (SD) $AUC_{0\text{-}Tmax}$ for the MAP/MPAP ratio was −0.29 (2.93), which was significantly lower ($P < 0.001$) than that in the iMil subgroup [3.94 (2.06)]. In the iMil subgroup, a positive correlation was found between the $AUC_{0\text{-}Tmax}$ for plasma concentrations and the AUC for the ratio ($r^2 = 0.414$; $P = 0.004$) (Fig. 4). In ten patients, an increase of > 20% of the MAP/MPAP ratio was observed.

Discussion

In this randomized clinical trial, the use of iMil was associated with a modest improvement in hemodynamic parameters; however, there were no differences in our primary clinical endpoint of difficult or complex separation from CPB. While the study may have been underpowered, as the differences between groups were so small, our findings suggest that the effect of iMil, if any, is likely to be similarly small. Our study also highlights that both EuroSCORE and RVESA are useful predictors of postoperative RV failure.

The hemodynamic effects of iMil were associated with increased CO through an increase or maintenance in stroke volume, which is in contrast with the control group where CO decreased. Nevertheless, no significant effects on heart rate or systemic arterial pressure were present. In addition, iMil was associated with a modest reduction (by 4.1 mmHg) in the hemodynamic severity of PH and a gradual reduction in right atrial dimension. The acute effect of iMil appears to be mediated through an increase in ventricular performance and a reduction in afterload. That being said, in accordance with a lower blood concentration than what is observed with intravenous loading, the acute effect of iMil appears to take place mostly through an increase in ventricular performance from increased contractility and a mild reduction in afterload. The effect on the reduction in the severity of PH was similar to Haraldsson's original description,[10] but the inotropic effect of iMil and its effect

Table 5 Intraoperative hemodynamic variables

	Group	T1 Intraoperative baseline	T2 End of nebulization	T3 20 min after CPB	T4 Chest closure	*P* value*	*P* value†
HR (beats·min^{-1})	Control	58(13)	67(17)	80(8)	82(6)	0.62	0.66
	Inhaled milrinone	60(15)	67(16)	79(10)	78(10)		
MAP (mmHg)	Control	73(11)	70(12)	69(10)	75(10)	0.58	0.93
	Inhaled milrinone	75(13)	71(20)	69(12)	74(14)		
CVP (mmHg)	Control	13(5)	12(5)	13(4)	15(4)	0.59	0.33
	Inhaled milrinone	12(6)	11(5)	12(6)	13(5)		
PAOP (mmHg)	Control	20(8)	18(6)	20(6)	21(5)	0.89	0.96
	Inhaled milrinone	18(8)	16(6)	18(5)	19(6)		
SPAP (mmHg)	Control	41(12)	39(13)	38(9)	41(9)	0.41	0.50
	Inhaled milrinone	39(13)	36(13)	37(11)	37(10)		
DPAP (mmHg)	Control	21(7)	19(8)	21(6)	23(5)	0.59	0.95
	Inhaled milrinone	19(9)	17(7)	18(7)	19(6)		
MPAP (mmHg)	Control	28(8)	26(9)	27(6)	29(6)	0.45	0.81
	Inhaled milrinone	26(10)	23(8)	24(8)	25(7)		
CO (L·min^{-1})	Control	3.3(1.0)	3.5(1.1)	4.3(1.3)	4.3(1.3)	0.03	0.27
	Inhaled milrinone	3.1(0.8)	3.5(1.2)	4.2(1.3)	3.9(1.2)		
Stroke volume (mL)	Control	58(19)	54(19)	55(19)	53(18)	0.01	0.14
	Inhaled milrinone	54(18)	56(22)	54(17)	51(16)		
MAP/MPAP	Control	2.83(0.87)	2.98(1.02)	2.72(0.79)	2.73(0.67)	0.88	0.99
	Inhaled milrinone	3.26(1.28)	3.38(1.47)	3.21(1.61)	3.22(1.37)		
PVR (dyne·sec^{-1}·cm^{-5}·m^{-2})	Control	230(195)	181(115)	131(61)	147(78)	0.82	0.48
	Inhaled milrinone	194(179)	157(96)	125(64)	127(63)		

Values represent mean (standard deviation). **P* value of the interaction term of the two-way repeated measures analysis of variance (ANOVA) model including T1 and T2. †*P* value of the interaction term of the two-way repeated measures ANOVA model including T1 to T4. CPB = cardiopulmonary bypass; CO = cardiac output; CVP = central venous pressure; DPAP = diastolic pulmonary artery pressure; HR = heart rate; MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; PAOP = pulmonary artery occlusion pressure; PVR = pulmonary vascular resistance; SPAP = systolic pulmonary artery pressure

on echocardiographic parameters have not been described. The reduction in right atrial dimension is consistent with previous observations where iMil was associated with an increase in atrial contractions in animals,[40,41] in human atrial tissues,[42] and in clinical trials[4] with reduced atrial dimension post-CPB.[17] Therefore iMil could also improve atrial contractile performance.

Exposure to iMil has been reported in 279 patients in small unblinded trials,[10,11,13-16] retrospective analyses,[12,19] in combination with $iPGI_2$,[18] and in case reports.[20-26] One trial involving 21 patients compared iMil (n = 11) with placebo.[17] In that study, the hemodynamic effect on MPAP was of similar magnitude.

Milrinone is a cyclic AMP-specific phosphodiesterase III inhibitor that can exert both positive inotropic effects and vasodilation independently of $ß_1$-adrenergic receptor stimulation in the cardiovascular system.[43] The major problem encountered with intravenous iMil is the high incidence of systemic hypotension resulting in an increased need for vasoactive drugs.[2,44-46] The hypotension resulting from intravenous iMil is caused either by vasodilation or through dynamic left ventricular (LV) or RV outflow tract obstruction.[47] Two randomized-controlled trials on the use of intravenous iMil in the non-cardiac surgical setting showed no advantage in terms of duration of hospitalization.[6,48] Furthermore, in the

Table 6 Intraoperative echocardiographic variables

Variables*	Group	T1 Intraoperative baseline	T2 End of nebulization	T4 Chest closure	*P* value*
RADt (cm)	Control	4.4(1.1)	4.4(1.1)	4.3(0.8)	0.88
	Inhaled Milrinone	4.1(0.8)	4.2(0.9)	4.0(0.7)	
RVD1 (cm)	Control	3.3(0.7)	3.4(0.7)	3.1(0.7)	0.55
	Inhaled Milrinone	3.2(0.7)	3.2(0.6)	3.0(0.8)	
RVD2 (cm^2)	Control	3.8(0.7)	3.9(0.9)	3.8(0.7)	0.65
	Inhaled Milrinone	3.7(0.7)	3.7(0.8)	3.7(0.7)	
RVD3 (cm)	Control	7.1(1.1)	7.0(1.2)	7.1(1.2)	0.66
	Inhaled Milrinone	6.8(1.1)	6.8(1.2)	6.8(1.1)	
RVEDA	Control	20.2(5.6)	20.2(7.6)	20.0(6.3)	0.77
	Inhaled Milrinone	19.1(6.6)	19.6(7.4)	18.9(6.2)	
RVESA	Control	11.1(3.80)	11.0(5.2)	11.6(4.7)	0.46
	Inhaled Milrinone	10.5(5.1)	10.3(5.2)	11.0(4.7)	
RVFAC	Control	45.4(8.4)	46.7(9.4)	43.1(9.4)	0.57
	Inhaled Milrinone	46.2(10.6)	49.1(11.3)	43.4(10.3)	
TAPSE (cm)	Control	1.9(0.6)	2.0(0.5)	1.5(0.5)	0.54
	Inhaled Milrinone	1.8(0.52)	1.9(0.5)	1.4(0.4)	

Values represent mean (standard deviation). **P* value of the interaction term of the two-way repeated measures ANOVA model

RADt = right atrial transverse diameter; RVD1 = right ventricular dimension at the level of the tricuspid annulus; RVD2 = transverse diameter of the mid-right ventricle; RVD3 = apical to annular right ventricular distance; RVEDA = right ventricular end-diastolic area; RVESA = right ventricular end-systolic area; TAPSE = tricuspid annular plane systolic excursion

PROMISE trial, patients receiving intravenous iMil experienced more adverse events and an increase in mortality.[48] A meta-analysis in cardiac surgery showed a trend in higher mortality in those exposed to intravenous iMil.[7]

In this study, we confirmed that postoperative RV failure was associated with a significant increase in mortality. Nevertheless, this mortality rate is lower than that reported in the TACTICS trial, which was 37%.[36] Despite similar inclusion criteria, the baseline SPAP in the TACTICS trial was higher, but no echocardiographic data were available. Interestingly, the importance of baseline RV function and dimension as preoperative predictors of RV failure was confirmed.[49] When using logistic regression, neither baseline SPAP nor MPAP was predictive of RV failure. Instead, the impact of PH on RV dimension or the baseline RVESA was the only predictor consistent with our previous study.[49]

There are several study limitations that need to be addressed. First, the optimal dosage and concentration of iMil are based on limited data.[22,29,30] Jaski *et al.* studied intravenous iMil concentrations in patients with congestive heart failure and reported a concentration-related positive inotropic action.[5] The concentration at the lowest iMil dosage was < 156 ng·mL^{-1}, and as the dose was increased, the concentration rose to > 400 ng·mL^{-1}. The therapeutic range reported was 100-300 ng·mL^{-1}.[50] In cardiac surgical patients, Butterworth *et al.* observed that even concentrations < 100 ng·mL^{-1} might be associated with a cardiac index increase of $\geq$15%.[51] As we were able to confirm, iMil levels < 100 ng·mL^{-1} are unlikely to induce significant systemic hypotension in cardiac patients.[50]

Nguyen,[22] Gavra,[29,30] and Haglund[19] have measured iMil concentrations following nebulization in patients with an LV assist device. It is possible that the limited effect of iMil on PH could be secondary to a lower and ineffective concentration in some patients. Inhaled iMil is not very liposoluble, and as shown in Fig. 3, the blood concentration will equilibrate within 15 min. So far, we have not seen the effect of weight when we administer a standard dose, but it could be possible that we may observe a higher AUC in smaller patients. Further studies might be required in order to select the best dosage. The dosage could explain why the overall efficacy might be limited. In our experience, the peak concentration of iMil is reached within 20 min, which corresponds to the end of nebulization.[22] This explains why we assessed the hemodynamic effect between T1 and T2. Nevertheless, because endothelial function remained altered in animal models exposed to iMil for up to four hours, we were interested in analyzing its effect after CPB.[9]

Then again, we were unable to show any clinically relevant advantage with the use of this strategy. This can be explained by the multifactorial complexity of a difficult or complex weaning from CPB leading to RV failure. We have previously shown that hemodynamic instability after CPB is often the result of various mechanisms.[52] For instance, vasoplegia might not respond well to

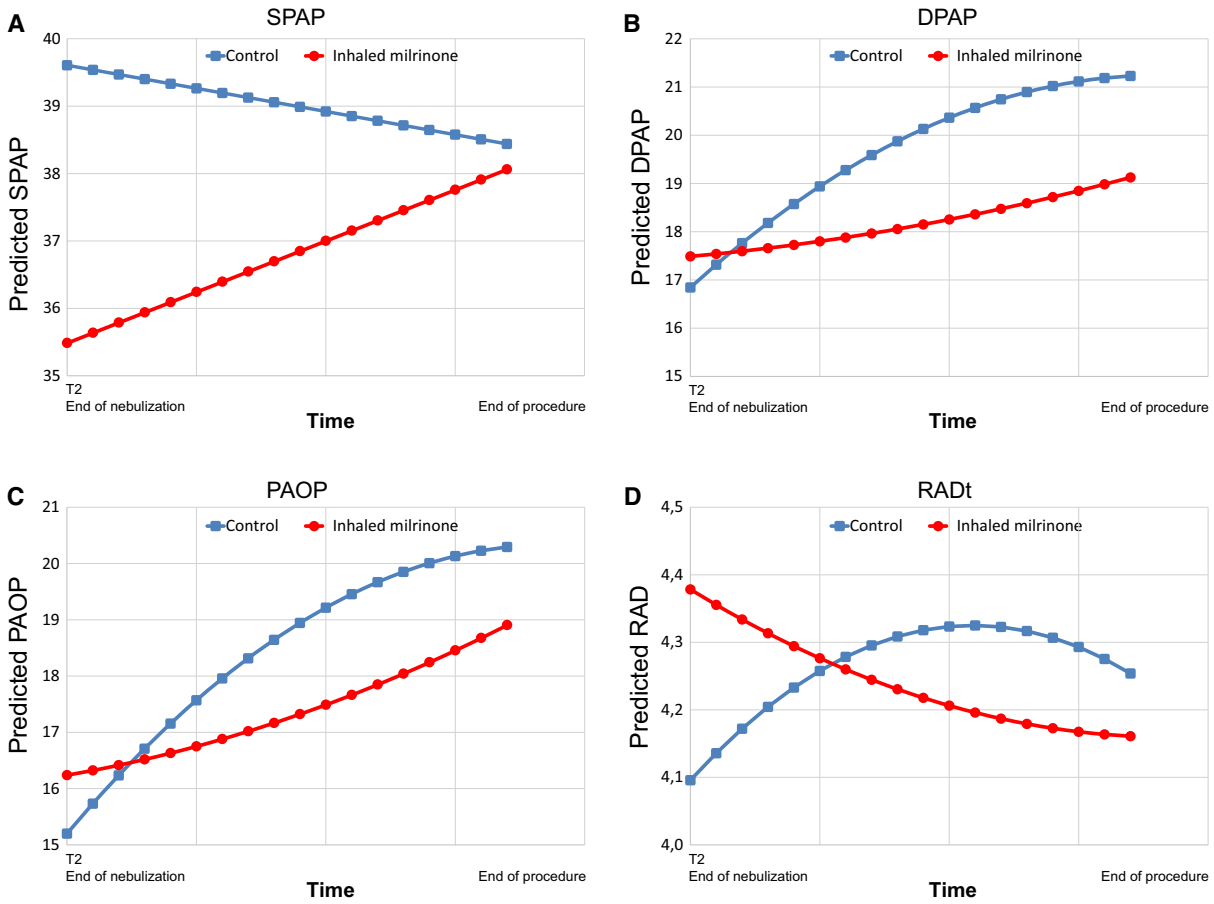

Fig. 2 The changes in (A) systolic pulmonary artery pressure (SPAP), (B) diastolic pulmonary artery pressure (DPAP), (C) pulmonary artery occlusion pressure (PAOP), and (D) right atrial transverse diameter (RADt) are shown from the end of nebulization (T2) to the end of the procedure over time on the X axis using linear mixed models. Using this model, baseline values and time are controlled. The predicted mean values of the variable are on the Y axis. Significant differences were noted in the evolution of only these hemodynamic and echocardiographic variables: linear effect with interaction for SPAP (P = 0.042), DPAP (P = 0.042), PAOP (P = 0.012), and RADt (P = 0.033) in the inhaled milrinone group compared with the control group

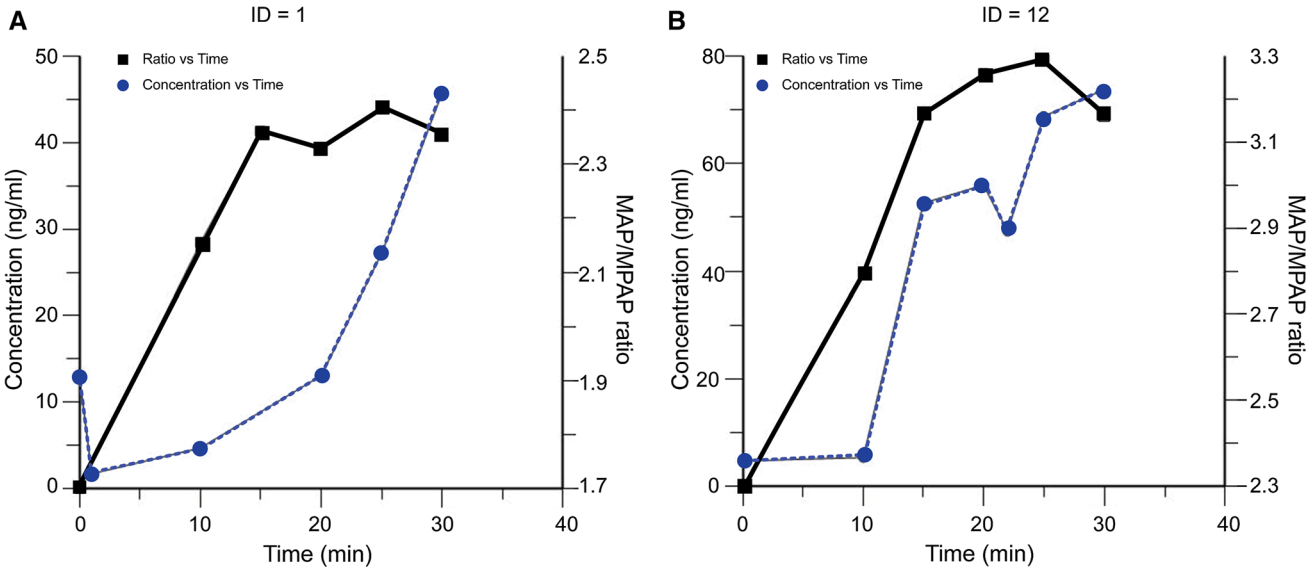

Fig. 3 Milrinone concentrations and the ratio between mean arterial pressure (MAP): mean pulmonary artery pressure (MPAP) from Patient #1 and #12 as a function time

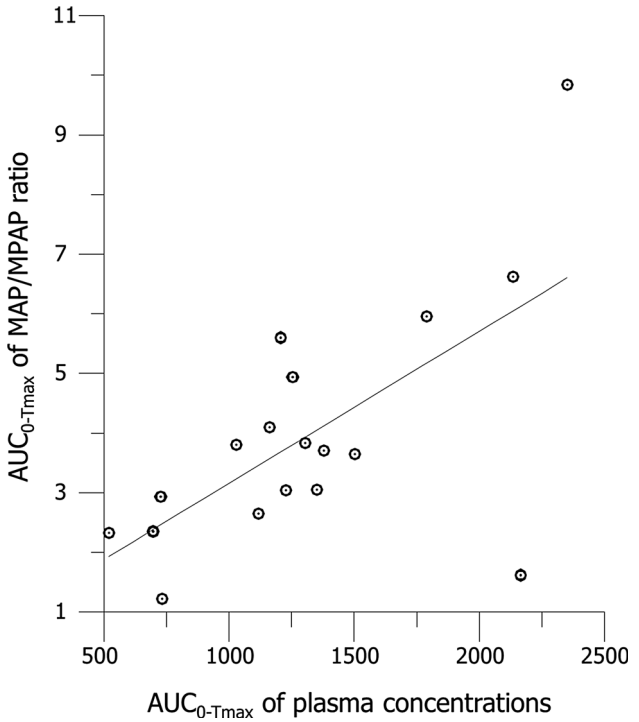

Fig. 4 Evolution of effect area under the curve (AUC) *vs* concentration AUC from time 0 to the time corresponding to the maximum concentration. MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure

iMil; however, in patients undergoing coronary revascularization[33] and valvular and complex surgery,[32] RV dysfunction is almost invariably present after CPB. In this study, RV failure was present in more than one-third (13/36) of those patients with difficult or complex separation from CPB. Therefore, strategies targeting improvement in RV performance without associated systemic hypotension might be relevant in cardiac surgery.

In addition, post-CPB PH is unlikely to be mediated only through cAMP mediators. For instance, endothelin-1 (ET-1) levels have been shown to correlate with the duration of CPB and postoperative complications.[53,54] Unfortunately, strategies towards controlling only the ET-1 pathway were also unsuccessful in the international TACTICS trial.[36] Therefore, future preventive or therapeutic strategies in PH and RV failure should consider combining therapies that would target multiple sites of action as previously reported.[10,18,24,55]

In summary, in high-risk cardiac surgical patients, iMil has favourable hemodynamic effect, no systemic hypotension, and is associated with an increased CO with a modest overall reduction in SPAP. Reduction in RV afterload after iMil can vary amongst patients and can be explained by variable PK/PD relationships. Nevertheless, a prophylactic strategy using iMil alone before CPB alone neither facilitates separation from CPB nor prevents post-CPB RV failure.

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