Preliminary experience with inhaled milrinone in cardiac surgery

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Abstract

Background: Inhaled administration of milrinone reduces pulmonary artery pressure. Pulmonary hypertension (PH) and right heart failure are associated with difficult separation from cardiopulmonary bypass (CPB). Therefore, inhaled milrinone could facilitate separation from CPB. Objective: To determine the impact and timing of administration of inhaled milrinone. Methods: A retrospective analysis of our experience on high-risk patients receiving inhaled milrinone was conducted to evaluate the postoperative course after administration of the drug. Results: Seventy-three patients received inhaled milrinone from June 2002 to February 2005. Mean age was 64 ± 13 years, with a mean preoperative Parsonnet score of 27 ± 14. Inhaled milrinone (5 mg) was administered before (n = 30) or after (n = 40) CPB, three patients had off-pump procedures and were excluded. CPB time was 145 ± 78 min with cross-clamping times of 91 ± 56 min without any significant difference between groups. Fifty-four patients (74%) had difficult separation from CPB, 14 patients (19%) required an extra-aortic balloon pump and 10 patients (14%) needed emergency reinitiation of CPB for hemodynamic instability. Ten patients died in the perioperative period (13.7%). Patients receiving inhaled milrinone prior to CPB initiation had a lowering pulmonary artery pressure after CPB (p < .01) and had less emergency reinitiation of CPB after weaning (3% vs 23%, p = .02) as compared to those with administration after CPB. No detectable side effects were directly linked to the administration of the drug. Conclusion: In this high-risk cohort, use of inhaled milrinone was well tolerated. Administration before initiation of CPB could help weaning from CPB.

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1. Introduction

Pulmonary hypertension (PH) is a frequent and morbid condition at the time of cardiac surgery [1,2]. Several preoperative conditions increase the risk of developing perioperative PH, including pre-existing PH, mitral stenosis or regurgitation and left ventricular dysfunction. Clinical strategies used clinically to treat perioperative PH include inhaled nitric oxide (iNO) [3–5], inhaled epoprostenol (iPGL2) [6–8] and intravenous phosphodiesterase inhibitors [9].

Milrinone is a type III phosphodiesterase inhibitor that increases intracellular concentration of cyclic adenosine monophosphate (cAMP) in the vascular smooth muscle cell and cardiomyocyte [10]. The effects of intravenous milrinone include pulmonary vasodilatation, systemic vasodilatation and increased inotropy. Milrinone is more efficient than placebo in facilitating weaning from cardiopulmonary bypass (CPB) [11] and is widely used in post-CPB left ventricular dysfunction and low cardiac output [12,13]. However, intravenous milrinone is associated with systemic hypotension and increased vasoactive drug requirements [14]. Moreover, in the largest randomized controlled trial studying the use of intravenous milrinone in the coronary care unit [15], no significant benefit in ischemic cardiomyopathy was observed [16]. The use of the inhaled route for milrinone was recently published in animal [17,18] and human studies [19,20]. As an alternative to nitric oxide and epoprostenol, inhaled milrinone does not require a complex setup, is less expensive, and no toxic metabolites need monitoring [21]. Furthermore, inhaled milrinone 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 to lower the pulmonary artery pressure without inducing systemic hypotension. In addition, administration of inhaled milrinone before and during CPB has been shown to be superior to the intravenous administration in...
reducing the pulmonary reperfusion syndrome [17], preventing pulmonary arterial endothelial dysfunction and improving oxygenation in a porcine model [17]. Only two studies describe the use of inhaled milrinone after cardiac surgery and in heart transplant candidates undergoing catheterization [19,20] with no significant side effect. However, in these studies, the timing of administration was constant and the effect on ventricular function using echocardiography was not evaluated. This report describes our preliminary experience with intraoperative use of inhaled milrinone and its effect on clinical outcome and ventricular function in 70 high-risk cardiac surgical patients. The main working hypothesis was that inhaled milrinone administered before CPB could be helpful for weaning of CPB in high-risk patients.

2. Methods

After approval from the local ethics and research committee and with the permission of Health Canada, a retrospective review of all the transesophageal echocardiograms of consecutive patients having received inhaled milrinone from June 2002 to February 2005 during cardiac surgery in a tertiary cardiac surgery center was conducted. All patients had preoperative risk assessment by Parsonnet and ASA scoring systems. Parsonnet scores of 0—4, 5—9, 10—14, 15—19, and >20 indicate progressively higher risks of mortality ranging from minimal (1%), mild (2%), and moderate (3%) to high (5%) and very high (5—10%) [2]. All patients were monitored by pulmonary artery catheter, electrocardiogram, pulse oximetry, capnography, and radial artery catheter. Anesthesia was induced with a fentanyl or sufentanil combination with midazolam and isoflurane according to the anesthesiologist’s preference. Blood cardioplegia was used in all patients. Induction and maintenance were cold to tepid (10—29 °C). The blood to crystalloidal ratio was 4:1. The pump flow was reduced to 0.5 l/min for aortic clamping and unclamping. The pumps for all patients were SIII (Stockert, Munchen, Germany) roller pumps. Oxygenator were Sorin Monolynth (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. Aortic procedures with circulatory arrest were done at 15—18 °C. Selective antegrade and retrograde cerebral perfusion were used on a case by case basis. Weaning from cardiopulmonary bypass was attempted after systemic temperature (central and vesical) was >36 °C.

CPB was established in 70 patients and 3 patients had off-pump procedures and were not included in the analysis. Postoperative management of pulmonary hypertension included intravenous nitroglycerine and milrinone and, in more severe cases, inhaled milrinone, epoprostenol or nitric oxide. Preoperative and operative characteristics were collected and postoperative hemodynamic status, events, weaning from CPB support, intensive care unit (ICU) and hospital stay, extubation time and mortality were analyzed according to the timing of the milrinone bolus. Difficult separation from bypass (DSB) was defined as systolic blood pressure <80 mmHg, confirmed by central measurement (femoral or aortic); pulmonary artery diastolic pressure (PADP) or pulmonary artery capillary wedge pressure (PCWP) >15 mmHg during progressive weaning from CPB; and the use of inotropic or vasopressor support (norepinephrine >4 μg/min, epinephrine >2 μg/min, dobutamine >2 μg/kg/min) for at least 1 h, intra-aortic balloon pump or CPB reinitiation [22]. Extreme difficult weaning from CPB was defined as the use of more than two inotropes, need for introduction of an intraaortic balloon pump (IABP) or reinitiation of CPB. The notion of extreme difficult weaning from cardiopulmonary bypass was introduced to identify very high-risk patients. Complex procedures were defined as reoperation, combined procedure, double valve procedure, operation for aortic dissection or endocarditis. The preoperative characteristics of the two groups were compared, and outcomes were analyzed to compare the effects of administration of inhaled milrinone before and after CPB.

2.1. Transesophageal echocardiography

After anesthesia induction, a multiplane TEE probe (Hewlett-Packard Sonos 5500, Andover, MA; Vivid 7 Imaging System, GE Healthcare, Amersh, USA) was inserted to obtain a standard sequence of cardiac images during a period of hemodynamic stability before pericardiotomy and again after sternal closure. Baseline and postoperative values were obtained according to published guidelines [23]. All TEE were performed by two anesthesiologists with more than 10 years experience and with National Board Certification. Global LV systolic function was evaluated by determining the fractional area change (FAC) which is equal to the difference between the end-diastolic and end-systolic area divided by the end-diastolic area obtained in a transgastric midpapillary view. Normal LV function was defined as FAC >50%. The FAC was collected as a categorical variable (above 50, 35—50 and below 35) and each patient was then compared to his preoperative status and classified as having an unchanged, worsened or improved FAC. To assess regional LV systolic function, the regional wall motion score index (RWMSI), using the 16 segments recommended by the American Society of Echocardiography, was measured using midesophageal 4-chamber, 2-chamber, and long-axis views as well as the transgastric midpapillary view (24). A rise in the RWMSI signifies a deterioration of the LV function.

2.2. Drug administration

Inhaled milrinone (Primacor, Sanofi-Synthelabo Canada Inc., Markham, ON, Canada) was administered through the endotracheal tube preceding the initiation of CPB [6,19] or upon discontinuation of CPB according to the surgical and anesthesiology team preference. Five milligrams (1 mg/ml) was administered, resulting in a dose ranging from 50 to 80 μg/kg, over 5 min. The study drug was administered through a jet nebulizer (Salter Labs, Arvin, CA) attached to the inspiratory limb of the ventilator near the endotracheal tube. Nebulization was achieved with a bypass flow of oxygen at 10 l/min. This high flow was used to achieve a high proportion of small particles. Since this added a secondary
flow to the patient, the minute ventilation was adjusted to maintain peak inspiratory pressures of less than 30 cm H\textsubscript{2}O.

2.3. Study groups

The patients were divided into two groups: those having received the inhaled milrinone before (BE, \(n = 30\)) and those receiving it after (AF, \(n = 40\)) CPB.

2.4. Statistical analysis

Patient characteristic results were expressed as mean \(\pm\) SD or simple frequencies and percentages. A logarithmic transformation was used when a continuous variable was not normally distributed. For continuous variables, comparison of groups was performed using the parametric (Student’s t-test) or nonparametric (Wilcoxon) test depending on the distribution. For categorical variables, comparison of groups was performed using Pearson chi-square test. Hemodynamic and regional wall motion score index values were measured before (BE) and after (AF) CPB.

3. Results

A total of 73 patients with a mean age of 64 \(\pm\) 13 years old, composed of 56% males were included. Seventeen patients had CAGB, 25 had valve procedures, 15 had combined valvular and CAGB, and 16 had other procedures (type A aortic dissection, left ventricular assist device insertion or ventricular repairs). Twelve patients had reoperative surgery (16%). Three patients were operated off pump and were not included in the analysis.

3.1. Preoperative (Table 1), operative (Table 2) and postoperative characteristics (Table 3)

Patients from groups BE and AF had similar preoperative characteristics and risk profile except for more diabetic patients in group BE \((p = .048)\). The Parsonnet scores (BE: 30.4 and AF: 26.1, \(p = .24\)), the type of procedures and the operative characteristics were similar among groups. Difficult weaning from CPB occurred in 73% and 80% of patients in group BE and AF, respectively. Nine patients from AF group necessitated reinitiation of CPB, as opposed to one from BE group patients \((p = .023)\). More patients in group AF necessitated adrenaline (5 vs 1), intravenous milrinone (7 vs 2), and IABP insertion (10 vs 4) than in group BE but the differences were not statistically significant.

3.2. Hemodynamic and oxygenation measurements (Table 4)

Mean pulmonary artery pressure (mPAP) decreased in the BE group while it increased in the AF group \((p = .009\) for interaction; \(p = .10\) and \(p = .03\) for comparisons in BE group.

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\*Table 1*

<table>
<thead>
<tr>
<th>Preoperative characteristics</th>
<th>Inhaled milrinone before CPB (BE) ((n = 30))</th>
<th>Inhaled milrinone after CPB (AF) ((n = 40))</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ((\pm SD))</td>
<td>(65 (\pm 11))</td>
<td>(63 (\pm 13))</td>
<td>(.50)</td>
</tr>
<tr>
<td>Male gender</td>
<td>19 (63)</td>
<td>22 (55)</td>
<td>(.48)</td>
</tr>
<tr>
<td>Weight ((\text{kg } \pm SD))</td>
<td>(79 (\pm 10))</td>
<td>(72 (\pm 17.0))</td>
<td>(.08)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 (57)</td>
<td>25 (63)</td>
<td>(.44)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11 (37)</td>
<td>6 (15)</td>
<td>(.048)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>8 (27)</td>
<td>13 (33)</td>
<td>(.5)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>8 (27)</td>
<td>13 (33)</td>
<td>(.46)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>8 (27)</td>
<td>13 (33)</td>
<td>(.5)</td>
</tr>
<tr>
<td>Left ventricular dilatation</td>
<td>12 (40)</td>
<td>16 (40)</td>
<td>(.86)</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>13 (43)</td>
<td>18 (45)</td>
<td>(.74)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>15 (50)</td>
<td>18 (45)</td>
<td>(.83)</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>18 (53)</td>
<td>21 (53)</td>
<td>(.69)</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>2 (7)</td>
<td>0 (0)</td>
<td>(.12)</td>
</tr>
<tr>
<td>LV FAC &lt; 35%</td>
<td>10 (33)</td>
<td>10 (25)</td>
<td>(.43)</td>
</tr>
<tr>
<td>Parsonnet score ((\pm SD))</td>
<td>(30.4 (\pm 14.2))</td>
<td>(26.1 (\pm 15.2))</td>
<td>(.24)</td>
</tr>
<tr>
<td>ASA score ((\pm SD))</td>
<td>(3.6 (\pm 0.8))</td>
<td>(3.6 (\pm 0.7))</td>
<td>(.94)</td>
</tr>
<tr>
<td>Emergency</td>
<td>9 (30)</td>
<td>12 (30)</td>
<td>(.98)</td>
</tr>
<tr>
<td>Preoperative IABP</td>
<td>2 (7)</td>
<td>2 (5)</td>
<td>(.77)</td>
</tr>
</tbody>
</table>

\*CPB*, cardiopulmonary bypass; \*SD*, standard deviation; \*ACE*, angiotensin converting enzyme; \*LV FAC*, Left Ventricular Fractional Area Change; \*ASA*, American Society of Anesthesiologists; \*IABP*, intraaortic balloon pump.
and AF group, respectively). Patients from both groups experienced a significant reduction in mean arterial pressure (MAP), a rise in heart rate and a rise in cardiac index after CPB with no statistically significant differences between the two groups. A deterioration of the MAP/mPAP ratio reflecting development of relative PH [24] was significantly more frequent in the AF group ($p = .01$), that group having a significant decline in MAP/mPAP ratio ($p < .0001$). Arterial

### Table 2
Operative characteristics

<table>
<thead>
<tr>
<th>Operation</th>
<th>Inhaled milrinone before CPB (BE) ($n=30$)</th>
<th>Inhaled milrinone after CPB (AF) ($n=40$)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG</td>
<td>13 (43)</td>
<td>20 (50)</td>
<td>.58</td>
</tr>
<tr>
<td>Reoperative procedure</td>
<td>6 (20)</td>
<td>6 (15)</td>
<td>.58</td>
</tr>
<tr>
<td>Complex</td>
<td>16 (53)</td>
<td>16 (40)</td>
<td>.27</td>
</tr>
<tr>
<td>Aortic valve replacement</td>
<td>15 (50)</td>
<td>13 (31)</td>
<td>.14</td>
</tr>
<tr>
<td>Mitral valve replacement</td>
<td>8 (27)</td>
<td>4 (10)</td>
<td>.07</td>
</tr>
<tr>
<td>LVAD insertion</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>.38</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>0 (0)</td>
<td>2 (5)</td>
<td>.21</td>
</tr>
<tr>
<td>Mitral valve repair</td>
<td>4 (13)</td>
<td>4 (10)</td>
<td>.7</td>
</tr>
<tr>
<td>Tricuspid valve repair</td>
<td>4 (13)</td>
<td>3 (8)</td>
<td>.42</td>
</tr>
<tr>
<td>Aortic procedure</td>
<td>5 (17)</td>
<td>8 (20)</td>
<td>.72</td>
</tr>
<tr>
<td>Left ventricular remodelling</td>
<td>0 (0)</td>
<td>2 (5)</td>
<td>.21</td>
</tr>
<tr>
<td>CPB time (min $\pm$ SD)</td>
<td>127.9 (±53)</td>
<td>156.7 (±93)</td>
<td>.16</td>
</tr>
<tr>
<td>Cross clamp (min $\pm$ SD)</td>
<td>77.8 (±31.7)</td>
<td>99 (±67)</td>
<td>.15</td>
</tr>
</tbody>
</table>

CPB, cardiopulmonary bypass; SD, standard deviation; IABP, intra-aortic balloon pump; CABG, coronary artery bypass graft; LVAD, left ventricular assist device.

### Table 3
Postoperative characteristics

<table>
<thead>
<tr>
<th>Operation</th>
<th>Inhaled milrinone before CPB (BE) ($n=30$)</th>
<th>Inhaled milrinone after CPB (AF) ($n=40$)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-CPB IABP insertion</td>
<td>4 (13)</td>
<td>10 (25)</td>
<td>.2</td>
</tr>
<tr>
<td>Difficult weaning from CPB</td>
<td>22 (73)</td>
<td>32 (80)</td>
<td>.51</td>
</tr>
<tr>
<td>Extreme difficult weaning from CPB</td>
<td>3 (18)</td>
<td>14 (82)</td>
<td>.02</td>
</tr>
<tr>
<td>Noradrenaline dose (µg/min ± SD)</td>
<td>9.9 (±8.5)</td>
<td>13.1 (±17.6)</td>
<td>.3</td>
</tr>
<tr>
<td>LV FAC &lt; 35%</td>
<td>5 (16)</td>
<td>10 (25)</td>
<td>.39</td>
</tr>
<tr>
<td>CPB reintitration</td>
<td>1 (3)</td>
<td>9 (23)</td>
<td>.023</td>
</tr>
<tr>
<td>Vasopressors more than 24 h</td>
<td>14 (47)</td>
<td>10 (25)</td>
<td>.07</td>
</tr>
<tr>
<td>ICU LOS (d ± SD)</td>
<td>5.6 (±5.8)</td>
<td>5.3 (±7.5)</td>
<td>.38</td>
</tr>
<tr>
<td>Hospit LOS (d ± SD)</td>
<td>15.2 (±14.1)</td>
<td>12.5 (±10.6)</td>
<td>.32</td>
</tr>
<tr>
<td>Intubation time (h ± SD)</td>
<td>48 (±109)</td>
<td>100 (±238)</td>
<td>.6</td>
</tr>
<tr>
<td>Mortality</td>
<td>3 (10)</td>
<td>7 (18)</td>
<td>.38</td>
</tr>
</tbody>
</table>

CPB, cardiopulmonary bypass; SD, standard deviation; LV FAC: Left Ventricular Fractional Area Change; ICU, intensive care unit; LOS, length of stay. IABP, intra-aortic balloon pump.

### Table 4
Hemodynamic response to surgery in milrinone before (BE) versus after CPB (AF)

<table>
<thead>
<tr>
<th>Operation</th>
<th>Inhaled milrinone before CPB (BE) ($n=30$)</th>
<th>Inhaled milrinone after CPB (AF) ($n=40$)</th>
<th>Interaction group × time p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP before CPB (mmHg)</td>
<td>80 (±11)</td>
<td>80 (±19)</td>
<td>.68</td>
</tr>
<tr>
<td>MAP after CPB (mmHg)</td>
<td>72 (±8)</td>
<td>71 (±11)</td>
<td></td>
</tr>
<tr>
<td>PaO$_2$/FiO$_2$ before CPB</td>
<td>353 (±141)</td>
<td>391 (±88)</td>
<td>.60</td>
</tr>
<tr>
<td>PaO$_2$/FiO$_2$ after CPB</td>
<td>262 (±119)</td>
<td>285 (±98)</td>
<td></td>
</tr>
<tr>
<td>HR before CPB (bpm)</td>
<td>68 (±16)</td>
<td>72 (±24)</td>
<td>.87</td>
</tr>
<tr>
<td>HR after CPB (bpm)</td>
<td>74 (±12)</td>
<td>79 (±16)</td>
<td></td>
</tr>
<tr>
<td>CI before CPB (l/min/m$^2$)</td>
<td>1.9 (±0.6)</td>
<td>2.1 (±0.4)</td>
<td>.44</td>
</tr>
<tr>
<td>CI after CPB (l/min/m$^2$)</td>
<td>2.6 (±0.5)</td>
<td>2.7 (±0.8)</td>
<td></td>
</tr>
<tr>
<td>mPAP before CPB (mmHg)</td>
<td>30 (±10)</td>
<td>25 (±8.5)</td>
<td>.009</td>
</tr>
<tr>
<td>mPAP after CPB (mmHg)</td>
<td>27 (±7)</td>
<td>28 (±8)</td>
<td></td>
</tr>
<tr>
<td>MAP/mPAP before CPB</td>
<td>2.9 (±1.0)</td>
<td>3.7 (±1.2)</td>
<td>.01</td>
</tr>
<tr>
<td>MAP/mPAP after CPB</td>
<td>2.8 (±0.7)</td>
<td>2.7 (±0.8)</td>
<td></td>
</tr>
<tr>
<td>PVRI Before CPB</td>
<td>271.1 (±50)</td>
<td>176.0 (±46.6)</td>
<td>.09</td>
</tr>
<tr>
<td>PVRI After CPB</td>
<td>192.3 (±7)</td>
<td>167.7 (±5.3)</td>
<td></td>
</tr>
</tbody>
</table>

CPB, cardiopulmonary bypass; SD: standard deviation; MAP, mean arterial pressure (mmHg); PaO$_2$/FiO$_2$, arterial oxygen partial pressure divided by inspired fraction of oxygen; HR, heart rate (beats per minute); CI, cardiac index (l/min/m$^2$); mPAP, mean pulmonary artery pressure (mmHg); MAP/mPAP, mean arterial pressure divided by mean pulmonary artery pressure. PVRI: Pulmonary Vascular Resistance Index (Dynes · s/cm$^5$m$^2$).
oxygen pressure divided by inspired O2 fraction (\(\text{PaO}_2/\text{FiO}_2\)) was lower after than before CPB (\(p < .0001\)) and similar between groups (\(p = .60\)).

3.3. Echocardiographic measurements

The evolution of left ventricular systolic function was significantly different between the groups. In the BE group, patients had a significant increased FAC (\(p = .002\)) compared to no change in FAC for group AF (\(p = .71\)). None of the patients experienced worsening of FAC in the BE group. Regional wall motion score index was similar among the two groups before (BE: 1.8 ± 0.6, AF: 1.5 ± 0.6) and after CPB (BE: 1.6 ± 0.6, AF: 2.0 ± 1.9) without any significant interaction (\(p = .12\)).

3.3.1. Univariate and multivariate analysis (Table 5)

Risk factors for mortality used in the univariate analysis were Parsonnet score, CPB time, aortic cross clamp time, postoperative IABP introduction and very difficult weaning from CPB. Administration of inhaled milrinone before CPB was not protective against mortality (\(p = .38\)). In the multivariate analysis, postoperative insertion of IABP was associated with increased mortality (OR = 17.7 CI: 3.7—84.5; \(p = .0003\)). Univariate analysis of risk factors for very difficult weaning from CPB showed that CPB and cross clamp times were significant predictors and that inhaled milrinone administration before CPB initiation (BE) was a protective factor (OR = 0.2, CI: 0.05—0.8; \(p = .02\)). Finally, in the multivariate analysis, only CPB time was a strong risk factor for very difficult weaning from CPB (OR = 1.02, CI: 1.007—1.03, \(p = .002\)).

4. Discussion

The major findings of this study are: (1) in high-risk patients with similar preoperative and operative characteristics, administration of a single bolus of inhaled milrinone before CPB is associated with lower mPAP after CPB than post CPB administration; (2) maintains or improves LV systolic function; and (3) is associated with a lower rate of CPB reintiation compared to those receiving inhaled milrinone after CPB.

Only two reports addressing the role of inhaled milrinone and inhaled epoprostenol in cardiac surgery have been published so far [19,20]. In the first, the mPAP, transpulmonary gradient and pulmonary vascular resistance decreased only in patients with PH, defined as a mPAP above 30 mmHg. The dosage was 2 mg based on intravenous milrinone loading doses used in heart transplantation. In the second study, the demonstrated magnitude of the effect was similar to the previous study [19]. However, in both studies, the intraoperative usage and the timing of inhaled milrinone was not explored.

The present study reports our preliminary experience in patients having received inhaled milrinone through a similar mode of administration. The same clinical findings of reduced pulmonary artery pressure and higher MAP over mPAP ratio were observed when inhaled milrinone was administered before CPB. An animal study in our laboratory has shown that the reduced pulmonary artery pressure was secondary to a 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 [17]. Administration of milrinone before and, in smaller doses, during CPB through a more uniform distribution and penetration in the lung parenchyma could protect the pulmonary vasculature during the weaning from CPB when ischemia-reperfusion injury occurs. The duration of the effect of the preoperative dose of inhaled milrinone was longer than the 20 min reported by Haraldsson et al. [19]. Administration of the drug before CPB followed by CPB initiation and diversion of the blood from the pulmonary arterial bed could explain this longer duration as the drug would diffuse in poorly irrigated lung parenchyma during the CPB run. The duration of effect of inhaled milrinone has not been described in humans but is consistent with our animal experiments in which the effect of inhaled agents on vascular tone can be quantified after CPB [17].

This may explain why patients in the BE group had a lower mPAP after separation from CPB. These findings were not observed when the administration of the drug occurred after

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>OR</th>
<th>95% confidence interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parsonnet score</td>
<td>1.065</td>
<td>1.016—1.116</td>
<td>.009</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>1.016</td>
<td>1.005—1.028</td>
<td>.006</td>
</tr>
<tr>
<td>Cross clamp time (min)</td>
<td>1.017</td>
<td>1.003—1.031</td>
<td>.02</td>
</tr>
<tr>
<td>Very difficult weaning from CPB</td>
<td>11.7</td>
<td>2.6—52.99</td>
<td>.002</td>
</tr>
<tr>
<td>Intubation time (h)</td>
<td>1.007</td>
<td>1.002—1.01</td>
<td>.005</td>
</tr>
<tr>
<td>Postoperative IABP</td>
<td>17.7</td>
<td>3.7—84.5</td>
<td>.0003</td>
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<tr>
<th>Risk factor</th>
<th>OR</th>
<th>95% confidence interval</th>
<th>p-value</th>
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<td>17.7</td>
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<th>p-value</th>
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<td>Cross clamp time (min)</td>
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<td>.04</td>
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<td>Inhaled milrinone timing (BE)</td>
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<td>0.05—0.8</td>
<td>.02</td>
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</table>

Table 5. Univariate and multivariate analysis of risk factors of mortality and very difficult weaning from CPB.

OR, odds ratio; CPB, cardiopulmonary bypass; BE, inhaled milrinone before CPB; IABP, intra-aortic balloon pump.
The administration of milrinone before CPB could be advantageous as the drug would be distributed in mechanically ventilated lungs, without any significant atelectasis before CPB. In addition, as demonstrated in the animal model, inhaled milrinone could prevent the post-CBP reperfusion injury associated with PH [17]. This could explain the lower mPAP values and the improved left ventricular function after separation from CPB. Furthermore, the left ventricular preload may have been enhanced in patients receiving inhaled milrinone before CPB as it was reported with other vasodilators such as nitric oxide [25] and inhaled epoprostenol [19], however no changes in pulmonary capillary wedge pressure was observed after inhaled milrinone in the Haraldsson et al. [19] or Sablotzki et al. pilot study [20]. The improved left ventricular function could also be explained by a partial intravenous absorption of the drug even though no signs of systemic hypotension were reported. The improved LV function and lower right ventricular afterload have led to a lower proportion of reinitiation of CPB in patients receiving inhaled milrinone before CPB. A lower rate of IABP insertion was also observed in this group (13% vs 25% p = NS), supporting an easier weaning from CPB. The total mortality was 13.7% and was not statistically different between groups (10% vs 18%). The predicted mortality for patients with Parsonnet scores from 26 to 30 is 6—16% [2].

Univariate and multivariate analysis were performed to determine risk factors for very difficult weaning from cardiopulmonary bypass and mortality. The timing of administration of inhaled milrinone was not identified as a predictor of mortality in this limited number of high-risk patients in whom several other factors played a role. Univariate and multivariate analysis to examine the risk factors for extreme difficult weaning from cardiopulmonary bypass identified CPB time and cross clamp time as risk factors and inhaled milrinone administered before CPB was a protective factor. However, in the multivariate analysis, the small number of patients and events allowed identification of increased CPB time as only risk factor for extreme difficult weaning from CPB.

5. Limitations

This study represents a retrospective analysis of patients in whom inhaled milrinone was used as it was introduced in our practice. With growing experience, our indications for administration were refined and patients with preoperative pulmonary hypertension receive inhaled milrinone on a more regular basis. Although both groups were statistically similar in terms of preoperative risk, there is a potential selection bias as clinical judgment and experience influenced the decision for using the drug before or after CPB. The anesthesiologists performing TEE were not blinded to the timing of administration. However, this study is so far the largest experience with the clinical use of inhaled milrinone in cardiac surgery. Our data support its efficacy and suggest that it may be advantageous to administer inhaled milrinone before CPB. Nitric oxide and epoprostenol are other inhaled agents that can be used in patients to treat PH in cardiac surgery [3—6,8]. The nebulized administration of milrinone has the advantage of being simpler and cheaper than nitric oxide and epoprostenol inhalation. These issues make inhaled milrinone an attractive option in a cardiac operating room environment. Several issues must be clarified including the ideal timing, the duration of the effect, the optimal dosages, the maintenance administration and the advantages of the inhaled compared to the intravenous route. Randomized controlled trials will seek to answer these options.

6. Conclusion

In summary, administration of inhaled milrinone before CPB in high-risk patients facilitates separation from CPB. When PH is present and difficult weaning from CPB is anticipated, inhaled milrinone before CPB may represent a promising approach as an adjunct in the treatment of RV dysfunction and low cardiac output syndrome.

References


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