Preliminary Experience With Combined Inhaled Milrinone and Prostacyclin in Cardiac Surgical Patients With Pulmonary Hypertension

Maxime Laflamme, MD,* Louis P. Perrault, MD, PhD,* Michel Carrier, MD, MBA,* Mahsa Elmi-Sarabi, MSc,† Annik Fortier, MSc,‡ and André Y. Denault, MD, PhD†

Objective: **To retrospectively evaluate the effects of combined inhaled prostacyclin and milrinone to reduce the severity of pulmonary hypertension when administered prior to cardiopulmonary bypass.**

Design: **Retrospective case control analysis of high-risk patients undergoing cardiac surgery.**

Setting: **Single cardiac center.**

Participants: **Sixty one adult cardiac surgical patients with pulmonary hypertension, 40 of whom received inhalation therapy.**

Intervention: **Inhaled milrinone and inhaled prostacyclin were administered before cardiopulmonary bypass (CPB).**

Measurements and Main Results: **Administration of both inhaled prostacyclin and milrinone was associated with reductions in central venous pressure, and mean pulmonary artery pressure, increases in cardiac index, heart rate, and the mean arterial-to-mean pulmonary artery pressure ratio ($p < 0.05$), with no significant change in mean arterial pressure. The rate of difficult and complex separation from CPB was 51% in the inhaled group and 70% in the control group ($p = 0.1638$). Postoperative vasoactive requirement was reduced at 12 hours (35.9 *v* 73.7% $p < 0.01$) and 24 hours (25.6 *v* 57.9% $p < 0.05$) postoperatively in the combined inhaled agent group. Hospital length of stay and mortality were similar between the groups.**

Conclusion: **Preemptive treatment of pulmonary hypertension with a combination of inhaled prostacyclin and milrinone before CPB was associated with a reduction in the severity of pulmonary hypertension. In addition, a significant reduction in vasoactive support in the intensive care unit during the first 24 hours after cardiac surgery was observed. The impact of this strategy on postoperative survival needs to be determined.**

KEY WORDS: ***cardiac surgery, milrinone, epoprostenol, prostacyclin, cardiopulmonary bypass, pulmonary hypertension***

PULMONARY HYPERTENSION (PH) is associated with increased morbidity and mortality in patients undergoing cardiac surgery.[1,2] PH increases right ventricular (RV) work, which can lead to RV dysfunction after cardiopulmonary bypass (CPB). The presence of RV failure carries a poor prognosis, with high risk of perioperative mortality from 37% to 90%.[3–5]

Several pharmacologic agents can be used in cardiac surgery in order to reduce PH.[6] Prostacyclin (PGI_2) and a phosphodiesterase inhibitor (PDE), such as milrinone, have been used successfully for that purpose. However, intravenous administration is limited by systemic hypotension because of nonselective vasodilation and by hypoxemia through worsening of intrapulmonary shunt caused by inhibition of hypoxic pulmonary vasoconstriction.[7,8] When administered by inhalation, PGI_2 and milrinone appear to be selective pulmonary vasodilators comparable with inhaled nitric oxide (iNO).[9] Both agents decrease pulmonary artery pressure (PAP) without causing systemic hypotension. Administration of inhaled milrinone previously has been reported to be as effective as inhaled PGI_2 in its effects on the pulmonary vasculature in cardiac surgery.[10] Furthermore, co-aerosolization of PDE inhibitors with inhaled iloprost, a PGI_2 analog, have been described to markedly enhance the prostanoid-induced PAP decrease while maintaining the lung selectivity of the vasodilatory response.[11] Combined inhalation therapy with PGI_2 and milrinone has been used before CPB in animal experiments and in cardiac surgery at only a few centers with a small number of patients.[12–15] The combination of drugs was shown to be more effective in reducing PH than when used alone. However, only one study has evaluated the impact of using these medications on hemodynamic parameters,[12] and one case report documented the effect of combining the agents on hemodynamic, echocardiographic, and brain oximeter variables. Furthermore, experimental and human experience from this center has suggested that administration of inhaled PGI_2 or inhaled milrinone could prevent the pulmonary reperfusion injury observed after CPB and, consequently, could facilitate separation from CPB.[16–18]

The hypothesis of this retrospective study was that combined administration of PGI_2 and milrinone before CPB is efficacious in reducing the severity of PH without the undesired systemic vasodilatation. In addition, the authors wanted to explore if this strategy could have a beneficial effect on hemodynamic parameters and vasoactive requirements during the weaning of CPB and in the intensive care unit (ICU) in high-risk patients with PH.

METHODS

After approval from the local ethics and research committee, the authors retrospectively reviewed the files of 600 consecutive patients operated from December 2003 to October 2009 using a transesophageal echocardiography (TEE) database of the Montreal Heart Institute.[19] The inclusion criteria were patients with PH undergoing cardiac surgery with CPB in whom both inhaled PGI_2 and milrinone had been given before CPB. Patients were considered to have PH if systolic pulmonary

*From the *Department of Cardiac Surgery, †Department of Anesthesiology, Montreal Heart Institute and Université de Montréal; and ‡Department of Biostatistics, Montreal Health Innovations Coordinating Center, Université de Montréal, Montreal, Quebec, Canada.*

Supported by Fonds de la recherche du Québec en Santé, Montreal, Quebec, Canada and Montreal Heart Institute Foundation, Montreal, Quebec, Canada.

Address reprint requests to André Y. Denault, Department of Anesthesiology, Montreal Heart Institute, 5000 Belanger Street, Montreal, Quebec H1T 1C8, Canada. E-mail: andre.denault@gmail.com

1053-0770/2601-0001$36.00/0

http://dx.doi.org/10.1053/j.jvca.2014.06.012

artery pressure (SPAP) was greater than 30 mmHg or mean pulmonary artery pressure (MPAP) was greater than 25 mmHg estimated using Doppler echocardiography or central venous catheterization. The diagnosis of PH was confirmed in the operating room after insertion of a pulmonary artery catheter. A Parsonnet score was calculated for all patients.[1]

Normal RV function was defined using both the aspect of the hemodynamic RV waveform and echocardiographic criteria (Fig 1).[20] The RV pressure waveform was obtained from the pulmonary artery catheter (Paceport, Edwards Lifescience, Irvine, California). This continuous RV pressure waveform monitoring has been used to detect changes in RV function during cardiac surgery.[5,21,22] Normal RV function is associated with a rapid systolic pressure rise and no significant difference between the systolic RV pressure and the SPAP.[21] A normal RV diastolic slope typically is horizontal (<4 mmHg slope) because of the normal RV compliance, which is much higher than LV compliance.[23] Abnormal RV function typically is associated with an abnormal pressure waveform with delayed relaxation.[24]

Both RV systolic and diastolic function also were assessed with TEE using published guidelines.[25] Systolic function was evaluated using fractional area change and tricuspid annular plane systolic excursion. Diastolic function was evaluated using the hepatic venous flow (HVF). As previously described, a normal HVF has a normal systolic component with higher velocities than the diastolic component.[26] The atrial reversal velocities should be less than 50% of the systolic component.

Cerebral oxygen saturation was measured using near-infrared spectroscopy (NIRS) (INVOS 5100 Somanetics, Troy, Michigan) with two sensors placed on each side of the forehead of the patients as previously described.[27] Baseline rSO_2 values were obtained with the patient in a supine position, breathing a mixture of oxygen (2 L/min) and air with nasal prongs.

Prostacyclin (Flolan; Glaxo-Wellcome Inc., Mississauga, Ontario, Canada) was given as epoprostenol salt, 1.5 mg dissolved in sterile glycine buffer diluent, for a concentration of 15 μg/mL as previously described.[28] Each patient received 4 mL of a solution containing PGI_2. Five milligrams (1 mg/mL) of inhaled milrinone (Primacor, Sanofi-Synthelabo Canada Inc., Markham, Ontario, Canada) were administered, resulting in a dose ranging from 50 to 80 μg/kg over 5 minutes.[18] The dosage of these drugs was based on previous reports, the authors experience, and pharmacokinetic studies.[18,28–31] Both drugs were administered through an ultrasonic nebulizer attached to the inspiratory limb of the ventilator near the endotracheal tube (Fig 2). Administration started after baseline hemodynamic profile was obtained before CPB.

Preoperative and operative characteristics were collected as well as postinhalation and postoperative hemodynamic status during weaning from CPB support and at 12 and 24 hours postoperatively. Hospital length of stay and mortality were recorded. Separation from CPB was classified as easy when either no support or only one class of drug (vasoactive agents, inotropes, or vasodilators) was required. It was defined as difficult when two classes of drugs were used, when the first weaning attempt failed with resumption of CPB, or when the patient required mechanical devices, such as an intra-aortic balloon pump (IABP), to be weaned from CPB.[32]

In order to compare the hemodynamic effect of patients exposed to inhaled agents with that of patients unexposed to inhaled agents, 20 consecutive patients with PH selected from the same period of time (between 2004 and 2008) who were not exposed to any inhalation drugs were selected. These patients were part of the control group from previous trials on PH.[28,30]

Results are expressed as mean ± standard deviation or median (Q1, Q3) for continuous variables and as frequency (%) for categoric variables depending on their normal distribution. The two groups were compared using t test or Wilcoxon-Mann-Whitney test for continuous variables and Pearson chi-square test for categoric variables. Repeated measures ANOVA models were used to study the hemodynamic data across time and between groups. Models included time, group, and group X time interaction. If the interaction term was significant at the 0.05 level, then comparisons between groups at each time point and between time points within each group were done. A p value < 0.05 was considered statistically significant. Statistical analyses were performed with SAS version 9.2.

RESULTS

A total of 41 patients received both inhaled PGI_2 and milrinone before CPB. The preoperative, intraoperative and postoperative characteristics of the population are summarized

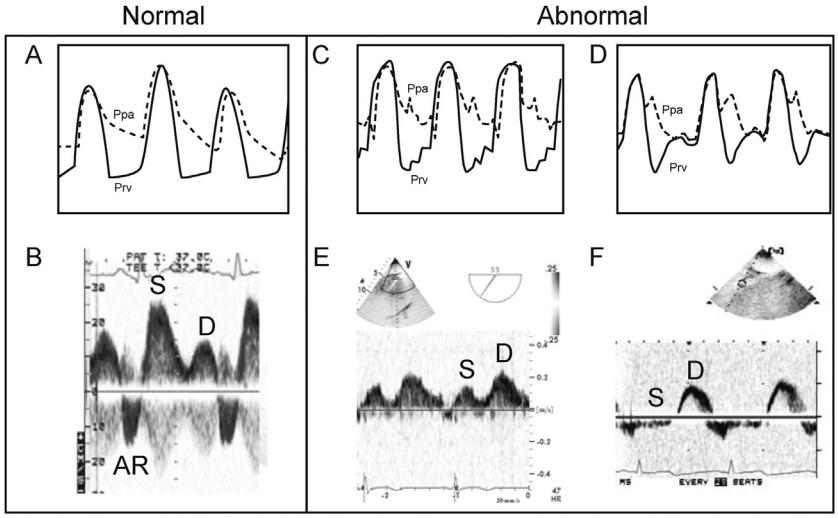

Fig 1. (A,B) Echocardiographic and hemodynamic definition for normal and abnormal (C-F) right ventricular function using hepatic venous flow (HVF) variables, right ventricular pressure (Prv), and pulmonary artery pressure (Ppa) (dotted line) waveforms. Note that as right ventricular function deteriorates, the Prv waveform changes from a (A) normal horizontal to an (C) oblique and then a (D) square root waveform. The latter is associated with Ppa diastolic equalization. Note also that as right ventricular function deteriorates, the S/D ratio > 1 (B) becomes < 1 (E) and the S wave flattens or can even become inverted (F) (AR, HVF atrial reversal; D, diastolic component of the HVF; S, systolic component of the HVF). (Adapted from Denault 2013[20]).