Cardiothoracic Anesthesia, Respiration and Airway

Inhaled iloprost controls pulmonary hypertension after cardiopulmonary bypass

[L'inhalation d'iloprost permet de contrôler l'hypertension pulmonaire après la circulation extracorporelle]

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Purpose: Severe pulmonary hypertension (PH) is a major cause of right ventricular (RV) dysfunction. Various iv vasodilator modalities have been used with limited results because of lack of pulmonary selectivity. The aim of the present controlled study was to evaluate the efficacy of inhaled iloprost, a synthetic prostacyclin analogue, in patients with elevated pulmonary vascular resistance (PVR) immediately after separation from cardiopulmonary bypass (CPB).

Methods: Twelve patients with persistent PH after discontinuation of CPB were included in the study. In all patients standard hemodynamic monitoring was used. Inhaled iloprost was administered via nebulized aerosol at a cumulative dose of $0.2 \mu\text{g}\cdot\text{kg}^{-1}$ for a total duration of 20 min. Complete sets of hemodynamic measurements were performed before inhalation (baseline), during and after cessation of the inhalation period. Echocardiographic monitoring of RV function was also used.

Results: Inhaled iloprost induced a reduction in the transpulmonary gradient at the end of the inhalation period in comparison to baseline (9.33 ± 3.83 mmHg vs 17.09 ± 6.41 mmHg, $P < 0.05$). The mean pulmonary artery pressure to systemic artery pressure ratio decreased over this period (0.28 ± 0.08 vs 0.45 ± 0.17 , $P < 0.05$). A statistically significant decrease of the PVR to systemic vascular resistance ratio was also observed (0.15 ± 0.05 vs 0.21 ± 0.05 , $P < 0.05$). Improved indices of RV function were observed in echocardiographic monitoring.

Conclusion: Inhaled iloprost appears to be a selective pulmonary vasodilator and may be effective in the initial treatment of PH and the improvement of RV performance in the perioperative setting.

Objectif : L'hypertension pulmonaire sévère (HP) est une cause majeure de dysfonction du ventricule droit (VD). Diverses modalités vasodilatatrices iv ont été utilisées et ont donné des résultats limités, étant donné le manque de sélectivité pulmonaire. Notre but était d'évaluer l'efficacité de l'inhalation d'iloprost, un analogue de la prostacycline synthétique, chez des patients qui présentent une résistance vasculaire pulmonaire (RVP) élevée immédiatement après le sevrage de la circulation extracorporelle (CEC).

Méthode : Douze patients présentant une HP persistante après l'interruption de la CEC ont été inclus dans l'étude. Une surveillance standard des paramètres hémodynamiques a été utilisée pour tous les patients. L'administration d'iloprost a été faite à l'aide d'un nébuliseur selon une dose de $0.2 \mu\text{g}\cdot\text{kg}^{-1}$ pendant au plus 20 min. Des ensembles complets de mesures hémodynamiques ont été réalisés avant l'inhalation (mesures de base), pendant et après la période d'inhalation. La surveillance échocardiographique de la fonction du VD a aussi été utilisée.

Résultats : L'iloprost inhalé a provoqué une réduction du gradient transpulmonaire à la fin de l'inhalation, en comparaison avec les mesures de base ($9,33 \pm 3,83$ mmHg vs $17,09 \pm 6,41$ mmHg, $P < 0,05$). Le ratio de la pression artérielle pulmonaire moyenne sur la pression artérielle systémique a diminué pendant cette période ($0,28 \pm 0,08$ vs $0,45 \pm 0,17$, $P < 0,05$). Une baisse statistiquement significative du ratio de la RVP sur la résistance vasculaire générale a été aussi observée ($0,15 \pm 0,05$ vs $0,21 \pm 0,05$, $P < 0,05$). Des indices supérieurs de la fonction du VD ont été observés par la surveillance échocardiographique.

Conclusion : L'inhalation d'iloprost semble être un vasodilatateur pulmonaire sélectif et pourrait être efficace comme traitement initial de l'HP et pour améliorer la performance du VD en période périopératoire.

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IMPAIRED right ventricular (RV) function due to elevated pulmonary vascular resistance (PVR) can make discontinuation of cardiopulmonary bypass (CPB) particularly laborious and urgent reinitiation of CPB is sometimes deemed necessary.¹

Research in recent years has been directed towards inhaled routes for the treatment of pulmonary hypertension (PH) as well as the introduction of new techniques to optimize drug delivery. The importance of pursuing the inhaled route for the treatment of PH lies in its selectivity for the lung as well as a decrease in the risk of systemic drug effects.^{2,3}

The aim of the present clinical study was to evaluate the efficacy of iloprost, a synthetic stable prostacyclin analogue in cardiac surgery patients presenting with severe RV dysfunction following discontinuation of CPB.

Materials and methods

The protocol of this non-blinded non-randomized study was reviewed and approved by the local Ethics Committee and informed consent was obtained. Exclusion criteria were a history of severe airway obstruction as well as an ejection fraction of less than 30%. The study subjects were pooled from an initial population of 50 patients with elevated pulmonary pressure as suggested by preoperative echocardiography indices. Increased transpulmonary gradient (TPG) after discontinuation of CPB (> 15 mmHg) accompanied by echocardiographic confirmation of isolated RV dysfunction was the cut-off point for iloprost administration. Twelve non-consecutive patients eventually fulfilled this criterion and consisted the study population.

On the morning of the operation, all patients received their regular doses of cardiac medications. They were all premedicated with oral lorazepam and ondansetron as well as *im* morphine 60–90 min before arrival in the operating theatre. After preoxygenation and a preanesthetic dose of midazolam, anesthesia was induced with etomidate, pancuronium and fentanyl. Anesthesia was maintained with oxygen in air with the addition of isoflurane in a volume-cycled ventilator. Normoventilation was ensured by serial blood gas evaluation. In addition to routine monitoring, which included radial and pulmonary artery catheters, a transesophageal echo (TEE) probe was placed into the esophagus (Vingmed T57S colour display monitor), after induction of anesthesia. No patient presented any contraindication for TEE probe insertion. Apart from standard hemodynamic variables measured or calculated, the intrapulmonary shunt and the transpulmonary

TABLE I Patient demographic and operative characteristics

Age (yr)	65 ± 17
Sex (M/F)	8/4
NYHA class	II:7/III:5
AVR	1
MVR	2
AVR/MVR	5
CABG	2
CABG/MVR	2
CPB duration (min)	129 ± 68
Operation duration (min)	270 ± 98

Values are expressed as mean ± SD. NYHA = New York Heart Association; AVR = aortic valve replacement; MVR = mitral valve replacement; CABG = coronary arterial bypass grafting; CPB = cardiopulmonary bypass.

pressure gradient were calculated using standard formulae. The TEE examination was performed by qualified anesthesiologists in consultation with cardiologists. Colour flow Doppler was used to evaluate valvular regurgitation.

CPB was initiated using an extracorporeal roller pump and a membrane oxygenator with a pump flow 1.8–2.5 L·min⁻¹·m⁻². All patients received the same anterograde and retrograde blood cardioplegia.

Iloprost was administered via a jet-nebulized device of aerosol generation. It was diluted in 0.9% saline to a concentration of 10 µg·mL⁻¹ and placed in a spacer connected to the inspiratory limb of the breathing circuit. Room air pressurization resulted in jet nebulization. A 20-min administration period produced a total cumulative dose of aerosolized iloprost between 9–21 µg.

Hemodynamic variables were evaluated at the following timepoints: before inhalation-baseline (T0), ten minutes after commencement of the inhalation period (T1), at the end of the inhalation period (T2) and ten minutes after the end of the inhalation period (T3).

Statistical analysis was performed by ANOVA for repeated measures and $P < 0.05$ was accepted as statistically significant. Results are reported as mean ± SD.

Results

Out of the 50 patients who consisted the initial study population a subset of seven patients with a left ventricular (LV) ejection fraction $< 30\%$ were treated with inotropic support and were excluded from the study. Demographic data of the 12 patients who fulfilled the criterion for post-CPB iloprost administration (TPG > 15 mmHg) are presented in Table I. During the initial attempt to wean these patients from CPB, the diagnosis of RV dysfunction was reinforced by characteristic TEE images such as localized akinesis of the

TABLE II Pulmonary and systemic hemodynamics pre- and post-iloprost inhalation

	T0	T1	T2	T3
MAP (mmHg)	89.82 ± 11.90	79.73 ± 9.21	77.40 ± 14.80	82.33 ± 17.84
MPAP (mmHg)	40.45 ± 11.24	29.27 ± 8.45*	25.40 ± 7.28*	23.00 ± 4.73*
MPAP/MAP ratio	0.45 ± 0.17	0.37 ± 0.11*	0.33 ± 0.12*	0.28 ± 0.08*
SVR (dyn·sec·cm ⁻⁵)	1561.45 ± 546.53	1149.27 ± 417.25	1149.90 ± 594.31	972.00 ± 223.50
PVR (dyn·sec·cm ⁻⁵)	303.82 ± 110.65	200.18 ± 106.28	158.10 ± 79.52*	152.17 ± 74.30*
PVR/SVR ratio	0.21 ± 0.05	0.19 ± 0.07	0.15 ± 0.06*	0.15 ± 0.05*
CI (L·min ⁻¹ ·m ⁻²)	2.25 ± 0.45	2.86 ± 0.69	2.82 ± 0.64	2.77 ± 0.50
TPG (mmHg)	17.09 ± 6.41	12.45 ± 5.34	10.70 ± 3.43*	9.33 ± 3.83*
HR (beats·min ⁻¹)	88.18 ± 21.38	87.00 ± 15.44	79.00 ± 13.96	83.33 ± 8.48
CVP (mmHg)	11.82 ± 4.53	10.18 ± 3.31	9.10 ± 3.07	9.15 ± 3.02
PCWP (mmHg)	16.92 ± 4.51	14.28 ± 3.92	15.00 ± 4.45	13.00 ± 3.46
IPSF (%)	10.82 ± 3.21	11.23 ± 4.65	10.89 ± 4.01	9.28 ± 3.23

T0 = before inhalation-baseline; T1 = ten minutes after commencement of the inhalation period; T2 = end of the inhalation period; T3 = ten minutes after the end of the inhalation period. MAP = systemic arterial pressure (mean); MPAP = pulmonary arterial pressure (mean); SVR = systemic vascular resistance; PVR = pulmonary vascular resistance; CI = cardiac index; TPG = transpulmonary gradient (MPAP-PCWP); HR = heart rate; CVP = central venous pressure; PCWP = pulmonary capillary wedge pressure; IPSF = intrapulmonary shunt fraction. Values are presented as mean ± SD, **P* < 0.05 in comparison to baseline.

RV apex and outflow tract or a markedly distended right atrium and ventricle. Isolated worsening tricuspid insufficiency was documented in four out of the 12 patients. LV dysfunction was not apparent on TEE examination, so LV dysfunction was excluded as a primary cause of PH.

After iloprost inhalation, selective pulmonary vasodilatation was demonstrated with a reduction of mean pulmonary artery pressure (MPAP) at the end of the inhalation period in comparison to baseline. A similar decrease in PVR was observed. Conversely, systemic blood pressure (MAP) and vascular resistance (SVR) were not affected (Figures 1–2). TPG dropped significantly whereas inhaled iloprost caused no statistically significant changes in other hemodynamic variables (Table II). We did not detect any alterations in oxygenation as depicted by serial blood samples and pulse oximetry.

Markedly reduced right chamber sizes were apparent in echo examination 20 min after iloprost administration whereas subsequent evaluation of videotaped echo material by blinded cardiologists to iloprost administration allowed for accurate calculation of objective indices of RV function like maximal tricuspid regurgitant jet velocity and RV percent change in area. The measurements revealed improvement of the above indices in comparison to pre-iloprost administration.

All our patients were eventually successfully extubated and discharged from intensive care unit. No major side-effects including any bleeding tendency were encountered for a four-day period of observation.

Discussion

Increased PVR may greatly complicate the perioperative management of cardiac surgical patients with a variety of independent factors usually implicated.⁴ The right ventricle is particularly susceptible to injury during the CPB and reperfusion periods.⁵

Inhaled iloprost, which is a stable prostacyclin analogue, seems to be an alternative promising approach in addressing the problem of post-CPB RV decompensation. The major advantage of inhalation therapy is the combination of the beneficial effects of prostacyclin with pulmonary selectivity thereby avoiding systemic side-effects and ventilation-perfusion mismatch. Our literature search was scarce regarding the use of nebulized iloprost in the perioperative setting.^{6–9} Therefore, we conducted the present clinical study aiming at evaluating the efficacy of iloprost on the urgent basis of post-CPB PH where prompt measures to unload the right ventricle should be expeditiously taken to ensure safe discontinuation of extracorporeal circulation.

The 12 patients included in the study demonstrated the characteristic hemodynamic profile of impending RV decompensation on the initial attempt of weaning from CPB. Measures attempting at remedying possible reversible factors were initiated. However, optimization of oxygen supply, prevention of light anesthesia and nitroglycerin administration did not improve the situation.

After iloprost inhalation, as our results demonstrated, selective pulmonary vasorelaxation was achieved with MPAP and PVR values decreasing significantly. Conversely, MAP and SVR values were not affected,

FIGURE 1 Mean pulmonary arterial pressure (MPAP)/mean systemic arterial pressure (MAP) ratio fluctuation over time, values as mean $\pm$ SD. * $P < 0.05$ in comparison to baseline.

FIGURE 2 Pulmonary vascular resistance (PVR)/systemic vascular resistance (SVR) ratio fluctuation over time, values as mean $\pm$ SD. * $P < 0.05$ in comparison to baseline.

suggesting that inhaled iloprost is selectively targeting the pulmonary circulation. Furthermore, the shunt fraction was not affected suggesting maintenance of gas exchange. In addition, the favourable hemodynamic response to iloprost application was further documented by TEE imaging.

The patients' subsequent uneventful course and improved indices of RV function on consecutive TEE imaging suggest that although hemodynamic effects of iloprost may be short-lived, other, yet unknown mechanisms affecting vascular remodeling may be involved in ensuring sustained beneficial effects.¹⁰

In summary, inhaled iloprost was used in our patients as a selective pulmonary vasodilator to optimize pulmonary hemodynamics without adverse systemic effects. Unlike *iv* prostaglandin,¹¹ it exerted a desirable preferential pulmonary vasodilatation with sustained postoperative benefits, the exact underlying mechanism of which remains to be further elucidated. With specific reference to the intraoperative setting, inhaled iloprost, provided by a system which is easy to assemble and always available in the operating theatre, may prove particularly valuable for selectively lowering RV afterload and facilitating CPB discontinuation in patients with RV dysfunction.

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