Inhaled iloprost to control pulmonary artery hypertension in patients undergoing mitral valve surgery: a prospective, randomized-controlled trial

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Background: Pulmonary hypertension (PHT) is common in patients undergoing mitral valve surgery and is an independent risk factor for the development of acute right ventricular (RV) failure. Inhaled iloprost was shown to improve RV function and decrease RV afterload in patients with primary PHT. However, no randomized-controlled trials on the intraoperative use of iloprost in cardiac surgical patients are available. We therefore compared the effects of inhaled iloprost vs. intravenous standard therapy in cardiac surgical patients with chronic PHT.

Methods: Twenty patients with chronic PHT undergoing mitral valve repair were randomized to receive inhaled iloprost (25 μg) or intravenous nitroglycerine. Iloprost was administered during weaning from cardiopulmonary bypass (CPB). Systemic and pulmonary haemodynamics were assessed with pulmonary artery catheterization and transoesophageal echocardiography. Milrinone and/or inhaled nitric oxide were available as rescue medication in case of failure to wean from CPB.

Results: Inhaled iloprost selectively decreased the pulmonary vascular resistance index after weaning from CPB (208 ± 108 vs. 422 ± 62 dyn·s/cm²/m², P < 0.05), improved the RV-ejection fraction (29 ± 3% vs. 22 ± 5%, P < 0.05), increased the stroke volume index (27 ± 7 vs. 18 ± 6 ml/m², P < 0.05) and reduced the transpulmonary gradient (10 ± 4 vs. 16 ± 3 mmHg, P < 0.05). In all patients receiving inhaled iloprost, weaning from CPB was successful during the first attempt. In contrast, three patients in the control group required re-institution of CPB and had to be weaned from CPB using rescue medication.

Conclusions: In patients with pre-existing PHT undergoing mitral valve surgery, inhaled iloprost is superior to intravenous nitroglycerine by acting as a selective pulmonary vasodilator, reducing RV afterload and moderately improving RV-pump performance.

Accepted for publication 13 July 2007

Key words: Right ventricular failure; mitral valve surgery; cardiopulmonary bypass; inhaled iloprost; pulmonary hypertension; pulmonary vascular resistance; right ventricular ejection fraction.

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PULMONARY HYPERTENSION (PHT) frequently complicates the perioperative management of patients undergoing mitral valve surgery (1). Pre-existing secondary PHT (mainly as a result of increased left atrial pressure and pulmonary vascular remodelling) may be aggravated by endothelial dysfunction related to cardiopulmonary bypass (CPB)-associated lung injury (2). Exacerbation of PHT may result in acute right ventricular failure (RVF), which has been demonstrated in cardiac surgical patients to be independently associated with high morbidity and mortality (3).

Strategies for treatment of PHT-related RVF primarily combine RV afterload reduction with positive inotropic support (4, 5). While the use of intravenous vasodilators is often limited due to subsequent arterial hypotension (1, 6), inhaled vasodilators offer the advantage of selective pulmonary vasodilation and are increasingly being used in the perioperative treatment of RVF.

Recently, inhaled iloprost as the stable analogue of prostacyclin (PGI₂) has been introduced into clinical routine in Europe. PGI₂ acts via specific endothelial receptors and activate the adenylate

Presented on the Annual Meeting of the European Association of Cardiothoracic Anaesthesiologists, Montpellier, France, June 1–4, 2005.
cyclase pathway, resulting in an up-regulation of cyclic adenosine 3',5'-monophosphate in the vascular smooth muscle cell with subsequent muscle relaxation and vasodilatation (7). The duration of action of iloprost has been described to last 30–60 min (8). While inhaled iloprost has been demonstrated to improve symptoms, pulmonary haemodynamics and prognosis in patients with idiopathic (primary) pulmonary arterial hypertension (9), evidence on the perioperative use of iloprost in cardiac surgery is mainly limited to case reports and observational studies (10–13). To our knowledge, only one randomized-controlled trial on the use of inhaled iloprost in patients undergoing pulmonary thrombendarterectomy, inhaled iloprost was shown to control residual PHT effectively in the post-operative period (14).

Hence, there is an important need for further evidence on the efficacy of inhaled iloprost in other subsets of cardiac surgical patients and for its use in the intraoperative period. We therefore compared the use of inhaled iloprost with standard intravenous treatment in a group of 20 patients with pre-existing secondary PHT and undergoing elective mitral valve repair. Inhaled iloprost was administered in a prophylactic approach already during weaning from CPB, in an attempt to prevent the occurrence of acute RVF.

We hypothesized that inhaled iloprost would improve pulmonary haemodynamics, RV function and subsequently the general haemodynamics in this selected group of high-risk cardiac surgical patients.

Methods

After institutional approval and written informed consent, 20 patients participated in this prospective, randomized and controlled trial. All patients were scheduled to undergo mitral valve repair (MVR) for severe mitral valve insufficiency degree 3+/4+ due to prolapse of the posterior leaflet (with or without concomitant coronary artery disease). The degree of mitral valve insufficiency had been estimated by transoesophageal echocardiography through the referring institutions. All patients were in New York Heart Association functional class III and suffered from secondary PHT (mean pulmonary artery pressure exceeding 25 mmHg as measured during pre-operative right heart catheterization or transoesophageal echocardiography) (15). The following exclusion criteria were used: emergency operation, atrial fibrillation, thromboembolic disease treated with anticoagulant therapy, severe renal or liver dysfunction, coagulopathy and thrombocytopenia.

Patients were randomly assigned to one of two groups, the intervention group receiving inhaled iloprost and the control group receiving intravenous nitroglycerine. Randomization was performed by means of a sealed envelope drawn by an independent person the day before surgery.

Anaesthesia

The patients were pre-medicated with 10 mg oxazepam orally in the evening before surgery and 1–2 mg flunitrazepam 1 h before arrival in the operating room. Pre-operative medication was continued until the day of surgery. General anaesthesia and muscle relaxation were induced with etomidate, 0.1 mg/kg, sufentanil, 0.5–2 μg/kg and rocuronium, 1 mg/kg. Maintenance of anaesthesia was accomplished with isoflurane, 0.5 MAC, and sufentanil, 2 μg/kg/h. During CPB, anaesthesia was maintained with sufentanil and midazolam, 0.05–0.1 mg/kg/h. Tidal volume and inspired oxygen concentration (FIO2) were adjusted to maintain normocapnia and arterial oxygen saturation > 95%.

Haemodynamic monitoring

Before induction of anaesthesia, a 5-F thermistor-tipped catheter (PV2015L20A, Pulsiocath, Pulsion Medical Systems AG, Munich, Germany) was inserted into the femoral artery. After induction of anaesthesia, a 7.5-F central venous catheter and an 8.5-F introducer sheath were placed in the right internal jugular vein. Via the latter, a 7-F pulmonary artery catheter (PV2047, VoLEF Catheter PACC 947, Pulsion Medical Systems AG) was inserted into the pulmonary artery under pressure guidance.

Routine haemodynamic variables (heart rate, mean arterial, pulmonary artery and central venous pressure) were recorded continuously (S/5, Datex-Ohmeda GmbH, Duisburg, Germany). Both the arterial thermistor catheter and the pulmonary artery catheter were connected to haemodynamic computers (PiCCOplus V 5.2.2 and VoLEF V 1.0, Pulsion Medical Systems AG) for the assessment of thermodilution curves allowing the discontinuous measurement of cardiac index (CI), stroke volume index (SVI) and right ventricular ejection fraction (REF) (16).

Indicator dilution measurements were performed by triple bolus injections of 20 ml of ice-cooled saline.
0.9% into the right atrium. Injections were randomly spread over the respiratory cycle. Each value represents the average of three measurements. The results were normalized to body surface area.

A multiplane transoesophageal echocardiography (TEE) probe (Omniplane II T6210, Philips Medical Systems, Eindhoven, the Netherlands) was introduced in all patients in order to visualize the transgastric short-axis view of the left ventricle at the level of the mid-papillary muscles. Images were digitally acquired on an ultrasonograph (Sonos 5500, Philips Medical Systems). For the estimation of cardiac contractility, left ventricular (LV) fractional shortening was determined using standard formulas. Simultaneously acquired TEE images and ECG signals were obtained before and after CPB and reviewed off-line by an experienced investigator blinded to the haemodynamic results. For each measurement, an average of at least four consecutive cardiac beats was evaluated.

Arterial and central venous blood samples were obtained for determination of haemoglobin content, lactate concentration, oxygen saturation and blood-gas analysis (ABL 700, Radiometer Copenhagen, Bronshøj, Denmark). Haemodynamic and blood-gas measurements were performed after induction of anaesthesia (T1), after pericardiotomy (T2), 15 min after CPB (T3) and after sternal closure (T4).

Surgery and CPB
All patients underwent median sternotomy. Mitral valve repair was performed during cardiopulmonary arrest in moderate hypothermia (32 °C nasopharyngeal temperature). The perfusion apparatus consisted of a roller pump (HL-20, Jostra, Hirrlingen, Germany) and a conventional oxygenator (Medos, Hi-Lite, Medos, Aachen, Germany) and was primed with an 1800 ml solution consisting of 500 ml HAES 10% (Fresenius, Germany) and 1000 ml Ringer’s lactate, 200 ml mannitol 20% and 100 ml NaHCO₃ 8.4%. Cardiopulmonary arrest was induced by infusion of 2000 ml of crystalloid cardiopulmonary solution into the aortic root (Custodiol™, Köhler Chemie, Alsbach-Hähnlein, Germany). In both groups, extracorporeal circulation was performed with a non-pulsatile pump flow of 2.2–2.41/min/m². As part of our clinical routine, 1,000,000 KIU aprotinin were administered before CPB, 1,000,000 KIU during CPB and 1,000,000 KIU after CPB. Before CPB, 300 U/kg heparin were administered to achieve an activated clotting time of >400 s. After weaning from CPB, heparin was antagonized with protamine. In all patients, mitral valve repair was performed with a combination of quadrangular resection of the middle scallop of the posterior leaflet and ring annuloplasty.

Study protocol
In both groups, basic fluid substitution was performed with 1 ml/kg/h balanced crystalloid solutions. In case of hypovolaemia (defined as a GEDI < 680 ml/m²), colloid solutions (hydroxyethylstarch 130/0.4, Voluven®; Fresenius Kabi, Bad Homburg v.d.H., Germany) were infused. Packed red blood cells were transfused when haematocrit was <24%. Arterial blood pressure during CPB was managed by fluid replacement (primarily with crystalloid solutions).

Patients in the intervention group received 25 μg of inhaled iloprost (Ilomedin®, Schering Deutschland GmbH, Berlin, Germany) during weaning from CPB at 50% pump flow. Iloprost was administered over 10 min via a commercially available nebulizer (Optineb, Nebu-tec, Elsenfeld, Germany) connected to the inspiratory limb of the ventilator circuit (17). Patients in the control group (n = 10) received IV nitroglycerine (0.5 μg/kg/min) after release of the aortic cross-clamp.

In both groups, cardiovascular therapy during and after weaning from CPB was tailored to reach pre-defined goals of haemodynamic stability: a CI of more than 2.51/min/m², a mean arterial pressure of more than 60 mmHg and a mixed venous oxygen saturation of more than 70%. Therefore, all patients in both groups received basic inotropic support with epinephrine 0.01–0.04/μg/kg/min. Norepinephrine, 0.01–0.05/μg/kg/min, was administered when the systemic vascular resistance index (SVRI) was below 1500 dynes/cm²/m² despite fluid replacement.

In case of low cardiac output during or immediately after weaning from CPB, milrinone 0.5 μg/kg/min was additionally started. When weaning from CPB failed due to RVF, a second period of CPB with 100% pump flow was initiated and 20 ppm inhaled nitric oxide (iNO) were administered together with milrinone. Thereafter, weaning from CPB was initiated again. Acute RVF was defined by TEE as a ratio between RV and LV end-diastolic area > 1 and concomitant low cardiac output (18).

Statistics
Pre-study power analysis was based on expected changes in the pulmonary vascular resistance
index (PVRI). Power analysis revealed a minimal sample size of eight patients to detect a 25% effect in PVRI when a level of significance of 0.05 and a power of 80% were to be achieved. The results were statistically analysed using a commercially available software package (Statistica© for Windows version 6.0, Statsoft, Tulsa, OK). Groups were compared by means of analysis of variance for repeated measurements (RMANOVA) with the within-group factor time and the between-group factor treatment (inhaled iloprost vs. standard care) (19). In case of significant differences, post hoc testing was performed using the Tukey–HSD test. A level of $P < 0.05$ was considered to be statistically significant.

**Results**

The demographic and baseline biometric data, cross-clamp time, duration of CPB and surgery time were similar among groups (Table 1). In both groups, simultaneous coronary artery bypass grafting was performed in three (Iloprost) and four (control) patients, respectively.

Before surgery, both groups were comparable with respect to systemic and pulmonary haemodynamics (Table 2). After weaning from CPB (T3), inhaled iloprost decreased PVRI (Fig. 1), reduced the transpulmonary gradient (TPG, i.e., the difference between the mean pulmonary artery pressure and pulmonary artery occlusion pressure) and increased REF (Fig. 2), stroke volume index and mixed venous oxygen saturation (Table 2) when compared with control. With the exception of REF, these effects could no longer be observed after sternal closure (T4).

Left ventricular fractional shortening was similar in both groups and did not change throughout the procedure. The mean arterial pressure and systemic vascular resistance showed a comparable decrease in both groups at T3 and T4. However, the ratio of pulmonary over systemic vascular resistance was significantly higher after CPB in the control group (Table 2). There were no differences in the use of epinephrine and norepinephrine between both groups at T3 and T4.

Weaning from CPB was successful during the first attempt in every patient receiving inhaled iloprost. No patient of the iloprost group required rescue medication consisting of milrinone or iNO according to our study protocol. In contrast, the primary attempt to wean from CPB failed in three patients of the control group due to the development of acute RVF. According to the protocol, a second CPB period with 100% pump flow was instituted. Weaning from CPB was then accomplished using a combination of iNO and milrinone. This procedure enabled successful weaning from CPB in two patients. Inhaled NO was titrated to the maximum reduction in RV afterload, resulting in concentrations of 20 and 40 ppm, respectively. In the third patient, weaning was performed only with i.v. milrinone and without iNO due to a technical problem with the delivery system.

There were no statistical differences in blood loss and need for transfusion between both groups. Within the first 24 h, iloprost patients lost 780 ml (490–1150 ml) via the chest tubes, whereas patients of the control group had a drainage of 720 ml (500–1250 ml) [mean (range)]. Iloprost patients received 1.8 (0–3) U of packed red blood cells, compared with 1.6 (0–3) units per patient in the control group [mean (range)]. Arterial blood-gas status was comparable in both groups (data not shown). In all patients, mitral valve repair was successfully performed and no conversion to mechanical valve replacement was needed.

**Discussion**

The results of the present study demonstrate that the application of inhaled iloprost during weaning from CPB effectively reduces RV afterload and moderately improves RV-pump performance in patients with pre-existing PHT undergoing mitral valve surgery.

The pathophysiology of PHT in mitral valve disease is complex. Increased left atrial pressures (in our patients indicated by increased pulmonary artery wedge pressure) result in chronic obstruction to venous drainage, in pulmonary vascular
remodelling and ultimately in pulmonary arterial vasoconstriction (20). In fact, all patients participating in the present study showed a considerable elevation of PVRI already under baseline conditions, associated with a significant impairment of RV-pump performance, as indicated by a low REF.

When undergoing cardiac surgery, pre-existing PHT is often aggravated in these patients due to a
variety of pathophysiologic processes. Both ischemia–reperfusion injury of the pulmonary vascular endothelium and the activation of inflammatory and vasoconstrictor cascades may result in exacerbation of pre-existing PHT (2).

Such an additional increase in afterload is poorly tolerated by the already compromised RV and may lead to acute RVF, which has been demonstrated to dramatically worsen outcome in cardiac surgical patients (3).

Therefore, treatment of PHT-associated RV dysfunction mainly focuses on pharmacological interventions that produce pulmonary vasodilatation (4, 5). Intravenous administration of vasodilators, however, almost invariably produces systemic vasodilatation and arterial hypotension, which, particularly in the haemodynamically unstable patient, further jeopardize RV function through a reduction of coronary perfusion and deterioration of ventricular interdependence (4, 21, 22). In contrast, inhalation of vasodilators has been shown to be an effective technique to obtain selective pulmonary vasodilatation. For a long time, inhalation of NO for selective pulmonary vasodilatation has been the gold standard in the perioperative setting (21). However, the inhaled administration of NO is technically cumbersome, may have toxic side effects and is associated with increasing costs (21). In addition, reports on the use of iNO show a large number of non-responders (23).

Inhalative administration of prostacyclin PGI2 has been proposed to be an alternative to iNO, because of lack of toxicity, ease of administration and significantly less costs (24–26). However, naturally occurring PGI2 has a short duration of action with a half-life of only 1–3 min, which requires continuous administration. Iloprost, the stable derivative of PGI2, has a longer duration of action and therefore enables intermittent use (7). Aerosolized iloprost has been shown to decrease RV afterload to a greater extent than iNO (27). In addition, inhaled iloprost was found to increase the clearance of endothelin in the pulmonary circulation (28). As the role of endothelin in CPB-related pulmonary vasoconstriction is increasingly being acknowledged (29), the use of iloprost in cardiac surgery may therefore be based on a further rationale.

In fact, a number of case reports and observational studies indicate that inhaled iloprost is effective in the treatment of acute RVF after heart transplantation, valve surgery and pulmonary thrombendarterectomy (10, 12, 13). However, up to now, no randomized-controlled trials are available in which the use of inhaled iloprost for the prevention of RVF has been studied in patients with PHT undergoing mitral valve surgery.

In our study, we could demonstrate that inhaled iloprost exerts selective pulmonary vasodilating effects when used in patients with secondary PHT during weaning from CPB. Interestingly, the mean arterial pressure and SVRI showed a comparable decrease in both groups after CPB, which is consistent with the finding that inhalation of iloprost shows a spill-over into the systemic circulation (8, 27). However, the ratio of PVRI over SVRI remained unchanged only after inhalation of iloprost, whereas in patients of the control group a significant increase was observed after weaning from CPB. This finding is most likely related to prevention of CPB-induced pulmonary vasoconstriction after CPB, which is in accordance with findings in patients with primary PHT and in patients undergoing heart transplantation (12, 30). Selective pulmonary vasodilation resulted in a significant reduction in RV afterload as indicated by a decrease in PVRI and in TPG, which may be of clinical relevance as TPG has been demonstrated to be a predictor of outcome in cardiac surgery (1, 31). The decrease in RV afterload was associated with an increase in REF and thus in RV pump performance, resulting in an increase in the stroke volume index immediately after CPB, compared with the baseline and with the control group (Table 2).

In addition, RVF requiring re-institution of CPB occurred in three out of 10 patients of the control group, whereas no patient in the iloprost group showed signs of RVF. Consequently, no second CPB period was necessary in patients receiving inhaled iloprost. To our knowledge, no prospective, controlled trials are available about the incidence of failure to wean from CPB in this high-risk group of cardiac surgical patients. Therefore, it is not possible to compare our data directly with those of other randomized trials. However, Fattouch et al. (1) demonstrated during the early post-operative period after mitral valve surgery that treatment with IV vasodilators had to be stopped in 62% of the patients due to severe systemic hypotension.

It has to be stressed that our study exhibits some important limitations. First, in view of the very limited size of the cohort, the trial was not sufficiently powered to assess clinically relevant endpoints like perioperative morbidity and mortality or failure to wean from CPB. However, intraoperative haemodynamics in the iloprost group were definitely not inferior to those of the control group.
acknowledgement

The Department of Anaesthesiology of the University of Aachen held a research grant from Schering AG, the manufacturer of Iloprost. W. B. and S. R. have received honoraria for lectures from Schering AG.

References


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