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Peri-Operative Pulmonary Hypertension in Paediatric Patients: Current Strategies in Children with Congenital Heart Disease

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Key Words
Congenital heart disease · Corrective surgery, CHD · Perioperative management · Pulmonary hypertension · Iloprost · Inhalation

Abstract
Congenital heart disease (CHD) is responsible for pulmonary hypertension (PH) in children in about 50% of cases. This pre-operative dynamic pulmonary hypertension can be superimposed and aggravated by acute post-operative PH or persist as chronic PH, especially in children who are not operated on early enough. Inhaled iloprost, a stable prostacyclin analogue, is used for the post-operative management of PH in infants and children with CHD. In a prospective open-label proof-of-concept study, the efficacies of inhaled nitric oxide (iNO) and inhaled iloprost were directly compared. Primary endpoints were the occurrence of a major or minor pulmonary hypertensive crisis. No significant difference between the effects of iNO versus iloprost on peri-operative PH was observed. Neither substance on its own prevented pulmonary hypertensive crises in high-risk infants, so a combination of both substances should be tested in future trials. In China, there are more than 4 million untreated CHD patients. More than 50% of them are untreated adults. Acute pulmonary vasoreactivity tests were performed in CHD patients between 9 months and 43 years of age using inhaled iloprost, in order to find out whether a pre-operative response to inhaled iloprost is a good predictor for the post-operative performance of these patients. The results showed that patient selection criteria for surgery should include both a 20% reduction in pulmonary vascular resistance (PVR) index after iloprost inhalation and a resulting PVR index <11 Wood U/m^2. CHD children between 14 days and 11 years of age took part in a placebo-controlled pilot study that investigated the role of aerosolized iloprost in the treatment of PH after corrective surgery. They received either low- or high-dose iloprost or placebo. Inhaled iloprost significantly improved haemodynamics in a dose-dependent manner and prevented reactive PH and pulmonary hypertensive crises in most of these mechanically ventilated children after CHD repair.

In infants and children with congenital heart disease (CHD; e.g. with large ventricular and/or atrial septal defect) a massive left-to-right shunt and therefore elevated pulmonary arterial pressure (PAP) is observed causing pulmonary hypertension (PH). This pre-operative dynamic PH can be superimposed and aggravated by acute post-operative PH. When the septal defect is closed by

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means of cardiac surgery during the first year of life, the pulmonary vasculature is, in general, restored to normal within 2–3 months (fig. 1). These children have an excellent quality of life and a normal life expectancy. They are not in danger of developing chronic PH.

However, in about 5% of patients post-operative complications occur. In these children, PH accompanied by low cardiac output persists or even worsens, so that they cannot be weaned from the ventilator. They have to be re-sedated and hyperventilated and need specific treatment. The mortality rate in these cases is about 20% [1].

Nitric oxide inhalation (iNO) is used for the post-operative management of PH in infants and children with CHD. It is considered to be effective, however, according to a Cochrane Database systematic review, its long-term efficacy with respect to mortality has not been confirmed [2].

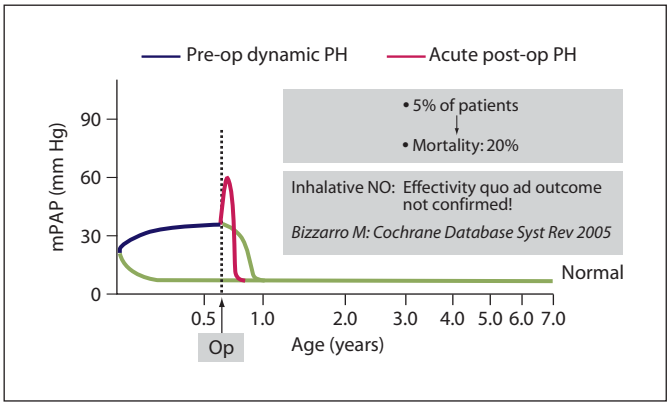

Fig. 1. PH in left-right shunt. mPAP = Mean pulmonary artery pressure. Modified from [1].

Prevention of Post-Operative PH: A Randomized Double-Blind Study of iNO versus Placebo

A randomized double-blind study showed that iNO is significantly more effective than placebo in preventing pulmonary hypertensive crises after congenital heart surgery. Altogether, 124 infants (median age 3 months) were randomly assigned to receive either continuous low-dose iNO or placebo, starting from surgery until just before extubation. Compared with placebo, infants receiving iNO had fewer pulmonary hypertensive crises and shorter times until criteria for extubation were met. The authors, therefore, concluded, that in infants at high risk of developing PH, routine use of iNO after congenital heart surgery can lessen the risk of pulmonary hypertensive crises and shorten the post-operative course, with no toxic effects [3].

This does not mean, however, that iNO should be used in every patient. A European consensus came to the conclusion that there is not sufficient evidence for the routine prophylactic use of iNO in neonates and children with cardiorespiratory failure. However, they recommended a trial using 20 ppm of iNO when significant post-operative PH is present [4].

Inhaled Iloprost in Children

One retrospective study investigated the short- and long-term outcome of 22 severely ill children with pulmonary arterial hypertension (PAH; idiopathic n = 12, CHD n = 10) that was not responsive to intravenous prostacyclin or subcutaneous treprostinil. The children were treated with inhaled iloprost. Acute administration of inhaled iloprost lowered mean pulmonary artery pressure (mPAP) by an amount equivalent to the response to iNO combined with oxygen. At 6 months, functional class improved in 35% of children. 64% of the patients continued receiving long-term iloprost therapy. Of 9 patients on chronic intravenous prostanoids, 8 transitioned from intravenous prostanoids to inhaled iloprost [5].

Two small observational studies showed that infants in a pulmonary hypertensive crisis after congenital heart surgery respond to inhaled iloprost [6], and that inhaled iloprost lowers the pulmonary to systemic arterial pressure ratio in children with CHD [7].

Comparison of iNO with Aerosolized Iloprost for Treatment of PH in Children after Cardiopulmonary Bypass Surgery

In order to get more information and to find more therapeutic options in these critically ill patients, a prospective open-label proof-of-concept study was undertaken that compared the efficacies of iNO and of inhaled iloprost. Infants older than 4 weeks but younger than 18 months of age with left-to-right shunt and PH pre-operatively and after cardiopulmonary bypass (CPB) surgery were recruited for this German investigator-initiated trial. Because the intention was to perform the study in the highest risk group, the investigators only included patients with mPAP >25 mm Hg immediately after weaning from the CPB at normal systemic pressure.

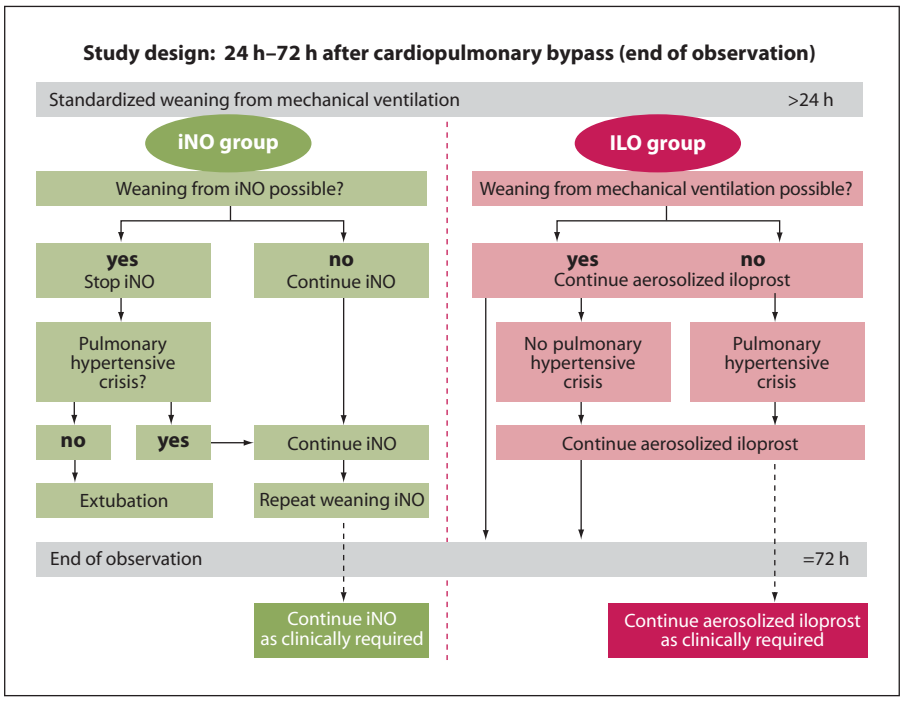

Fig. 2. Study design: comparison of iNO with aerosolized iloprost for the treatment of pulmonary hypertension in children after cardiopulmonary bypass surgery.

Study Design

Out of 224 patients treated, 15 fulfilled the predefined criteria and were randomized to receive either iNO (10 ppm) or iloprost (0.5 μg/kg/2 h via an ultrasound nebulizer). The study observation period comprised the first 72 h post-operatively (because thereafter it was intended to remove the pressure lines; fig. 2). Iloprost or iNO was started from surgery and continued as required clinically.

Weaning from mechanical ventilation was scheduled to take place 24 h after the operation or as soon as possible thereafter, because it is well known that if it takes too long to get the patient stable, he or she is at risk of developing secondary infections and may die from these infections and not from the primary disease.

Standard post-operative care in both study groups included analgesia and sedation (fentanyl 2–25 μg/kg/min; midazolam 1–4 μg/kg/min), intermittent positive pressure ventilation (hyperoxia: PaO_2 13.3–20.0 kPa; hyperventilation: pH 7.4–7.5), inotropic support as needed (epinephrine 0.05–1.0 μg/kg/min; dobutamine 5–15 μg/kg/min), and vasodilator drugs as needed (milrinone 0.5–1.0 μg/kg/min; sodium nitroprusside 0.5–2.0 μg/kg/min).

Haemodynamic monitoring was performed with arterial and PAP lines. Cardiac output was measured by thermodilution and using a PICCO system.

Primary endpoints were the occurrence of a major or a minor pulmonary hypertensive crisis. Major pulmonary hypertensive crisis was defined as a pulmonary to systemic arterial pressure ratio of >0.75, which means that the pulmonary pressure is raised to more than 3/4 of the systemic pressure as recorded by invasive arterial lines. Furthermore, a decline in the systemic arterial pressure exceeding 20% of the systemic arterial pressure before the event and a decline in the oxygen saturation had to be present. Minor pulmonary hypertensive crisis was also defined as a pulmonary to systemic arterial pressure ratio of >0.75, but no decline in the systemic arterial pressure exceeding 20% and no decline in the oxygen saturation had to be present.

Secondary endpoints were various haemodynamic parameters and the duration of the mechanical ventilation.

Results and Conclusion

Most of the 15 study patients were infants with Down syndrome and a large atrioventricular septal defect. The two study groups were comparable regarding age, weight, and haemodynamics. Pre-operative mean PAP was between 40 and 50 mm Hg in both groups.

Eight patients received iloprost and 7 patients received iNO. The post-operative pulmonary to systemic arterial pressure ratio exceeded 0.5 most of the time and, there-

fore, was too high in both study groups. The effects of iNO and of iloprost on the cardiac index and on the pulmonary vascular resistance (PVR) were comparable. The primary endpoint, the rate of pulmonary hypertensive crises, was comparable, too. Mean duration of mechanical ventilation was 12.9 days in the iNO group versus 13.1 days in the iloprost group.

Three children died between 14 and 125 days after the surgical procedure, one due to pneumonia and two due to their primary disease.

Thus, in this pilot study, there was no significant difference between the effects of iNO and of iloprost on perioperative PH. Neither substance on its own prevented major and minor pulmonary hypertensive crises in these high-risk infants. However, it was demonstrated that iloprost can be administered safely to intensive care infants. Therefore, larger trials using a combination of the two substances should be undertaken.

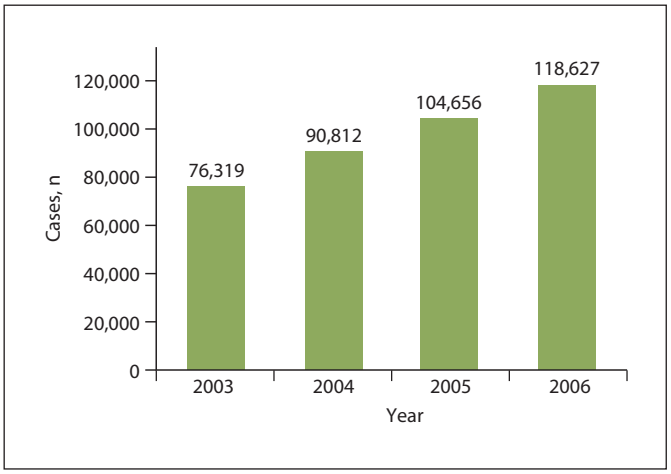

Fig. 3. Cardiovascular surgery in China. 55–60% are CHD surgery.

CHD: The Situation in China

Epidemiology

There are more than 4 million untreated patients with CHD in China. More than 50% of these CHD patients are untreated adults. Each year, 150,000 babies with CHD are born. In 2005, 653 hospitals with a cardiac surgery department existed in China. They employed about 3,600 cardiac surgeons and 300 paediatric cardiologists. In 2006, almost 120,000 cardiovascular surgical procedures were performed; 55–60% of these were CHD surgery (fig. 3), including around 20,000 interventional catheter cases for CHD per year.

Despite these impressive numbers, a large number of patients remain untreated or are treated very late. Many of these patients have PAH.

In the Beijing Anzhen Hospital, more than 5,000 patients undergo cardiac surgery each year, approximately half of them with and half of them without a cardiopulmonary bypass. In 2008, almost 1,300 patients with CHD, half of them children, were operated on in this hospital (fig. 4).

Pre-Operative Evaluation of Patients at Risk for Peri-Operative PAH

Because PAH is a risk factor for survival following surgery for CHD, it is very important to assess pulmonary vascular reactivity in patients with severe PAH prior to the surgical intervention.

Between July 2006 and December 2008, acute pulmonary vasoreactivity tests were performed in 46 patients between 9 months and 43 years of age with CHD (ventricular and/or atrial septal defect and/or patent ductus arteriosus Botalli) and severe PAH. The purpose of these tests was to distinguish between a reversible vasoconstriction and irreversible damage. Oxygen is usually used in Anzhen Hospital for the vasoreactivity tests, but the results are not very reliable and are not a good predictor for the post-operative performance of these patients. Therefore, a new vasodilator that would bring about more accurate results had to be found, and iloprost was chosen for this series.

During and after administration of 20 μg of iloprost for 15–20 min (10 μg in patients <15 kg bodyweight) using a facemask, PAP and systemic blood pressure were monitored continuously via right and left heart catheterization. Blood samples were drawn to measure haemodynamics at baseline and 30 min after iloprost inhalation. A positive reaction was defined as a reduction in PVR index of at least 20% compared to baseline without a decrease of the systemic blood pressure.

Results and Conclusion

Of the 46 patients, 29 showed a positive result after iloprost inhalation (table 1). Out of these 29 patients, 21 (72%) underwent successfully cardiac surgical repair with a reduction of mean pulmonary arterial pressure (mPAP) to an average of 27.11 ± 9.88 mm Hg after the operation. The duration of stay in the intensive care unit

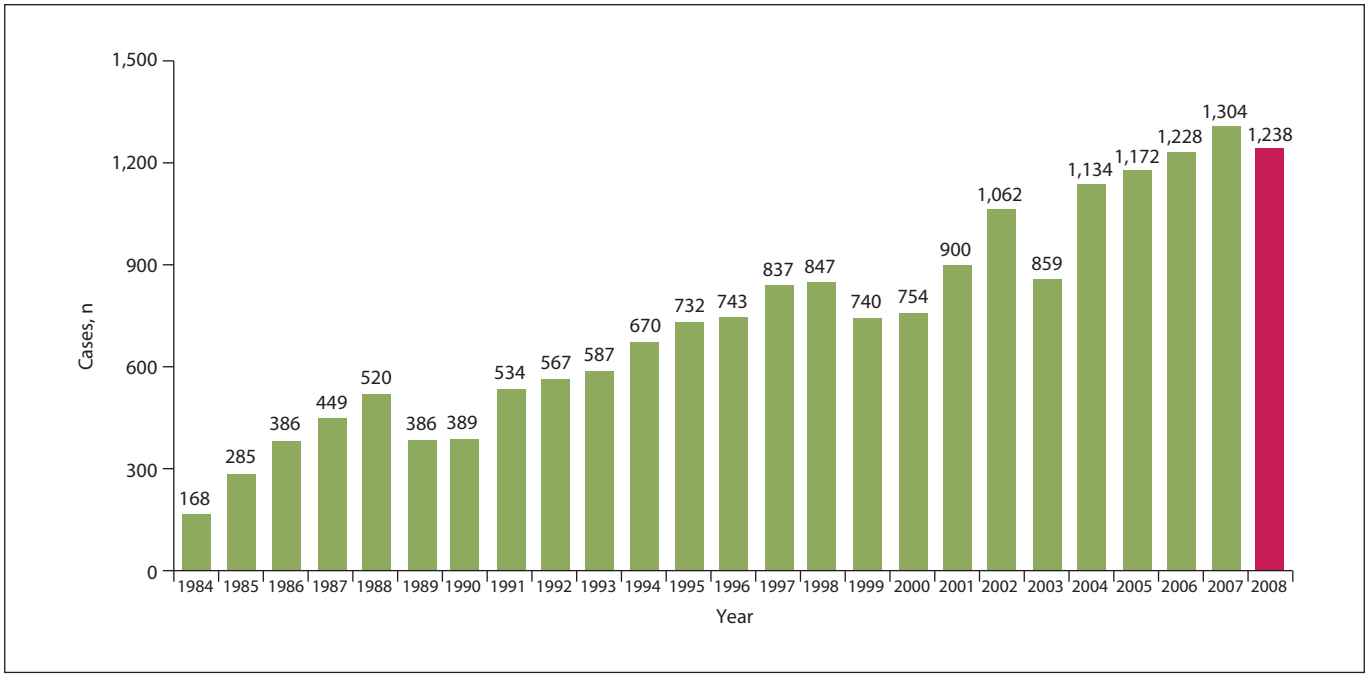

Fig. 4. CHD surgery in Anzhen Hospital, Beijing, China. Data include both children and adults. There were 18,491 cases completed in total.

Table 1. Haemodynamic changes with iloprost inhalation

	Positive group (n = 29)		Negative group (n = 17)	
	before iloprost inhalation	after iloprost inhalation	before iloprost inhalation	after iloprost inhalation
Mean pulmonary arterial pressure, mm Hg	71.4 ± 12.9	63.5 ± 12.6	83.6 ± 13.5	78.7 ± 14.5
Mean systolic blood pressure, mm Hg	86.7 ± 11.5	84.3 ± 11.0	88.2 ± 12.5	89.3 ± 11.9
Pulmonary artery wedge pressure, mm Hg	13.4 ± 4.0	13.5 ± 3.7	11.47 ± 2.1	11.7 ± 2.9
Pulmonary to systemic blood flow ratio (Qp/Qs)	1.8 ± 1.24	3.0 ± 1.5	1.1 ± 0.5	1.3 ± 0.5
Pulmonary vascular resistance index, Wood U/m^2	14.91 ± 5.98	8.92 ± 4.09*	21.41 ± 9.83	18.86 ± 8.64
Pulmonary to systemic resistance ratio (Rp/Rs)	0.53 ± 0.28	0.28 ± 0.16*	1.01 ± 0.51	0.89 ± 0.47

* $p < 0.05$.

was 2.12 ± 0.71 days. Only two of the 17 patients from the negative group were referred for surgery. One of these patients required prolonged post-operative mechanical ventilation that was complicated by pulmonary infection. After 3 years of follow-up, all surgically treated patients are alive.

Altogether, four of the surgically treated patients (the two from the negative group and two from the positive group) had a post-operative mPAP >45 mm Hg. The PVR index in these patients dropped by 11, 19, 26 and 33%, respectively, during the vasoreactivity test. However, the indices measured at the end of the vasoreactivity test were still between 11 and 16 Wood U/m^2.

It can therefore be concluded that inhaled iloprost selectively lowered the PVR as monitored by cardiac catheterization. The substance was safe and easy to adminis-

ter even in young children. Thus, iloprost may be a good choice for assessing pulmonary vascular reactivity. However, the criteria for selecting patients for surgery should be amended to include both a 20% reduction in PVR index after iloprost inhalation and a resulting PVR index <11 Wood U/m^2.

Iloprost for PAH after Paediatric Congenital Heart Defect Corrective Surgery: A Chinese Pilot Study

CHD is responsible for PH in children in about 50% of cases [8]. Right-heart failure, hypoxaemia, circulatory collapse, or pulmonary hypertensive crises are the major post-operative complications in CHD patients. Data from Boston showed that PH alone is responsible for 8% of post-operative deaths in CHD patients [9]. In the Shanghai Children's Medical Center, more than 3,000 children undergo heart surgery per year, among them about 500 children with PH. The incidence of complex (not simple, shunt-mediated) cases of post-operative reactive PH or pulmonary hypertensive crises is approximately 14%. The mortality of these patients is almost 12%.

Until December 2004, inhaled NO was used post-operatively in life-threatening conditions, and, in a small study, showed a response of approximately 90%. However, because NO is not regularly used in medical treatment in China and its administration is discussed controversially, an alternative had to be found. In a direct comparison in children between 1 and 10 years of age, aerosolized iloprost proved to be as effective as iNO in selectively lowering PVR in an acute haemodynamic study [10]. Therefore, aerosolized iloprost was chosen to be tested as an alternative to iNO for the post-operative treatment of acute PAH in these children.

Trial Design

Altogether, 64 ventilator-dependent children between 14 days and 11 years of age took part in the pilot study that investigated the role of aerosolized iloprost as a selective pulmonary vasodilator in the treatment of PH in CHD-children after corrective surgery. The trial was prospective and placebo-controlled. Older children (>4 years of age) with shunt-mediated PH as well as younger children with complex PH were included. Other inclusion criteria were congestive heart failure, a reduced exercise tolerance, a peripheral blood oxygen saturation (SpO_2) <92%, a pulmonary to systemic arterial pressure ratio (Pp/Ps) >0.75, a pulmonary to systemic blood flow ratio (Qp/Qs) <1.5, and a PVR >9 Wood U.

Most of the children (19%) had a dextro-transposition of the great arteries or (17%) a double outlet right ventricle together with a ventricular septal defect. Only 8 patients had a single defect such as a ventricular septal defect or a patent ductus arteriosus Botalli. For intra- and post-operative monitoring, a central venous line, a left atrial catheter, and a pulmonary artery catheter were inserted. Continuous cardiac output was measured using a PICCO system. The children weighed between 2.5 kg and 26 kg and were randomized to receive either low-dose iloprost (30 ng/kg/min) or high-dose iloprost (50 ng/kg/min) or placebo, given for 10 min every 4 h during the first 48 h after surgery (fig. 5). Thereafter, weaning the patients off the ventilator was started.

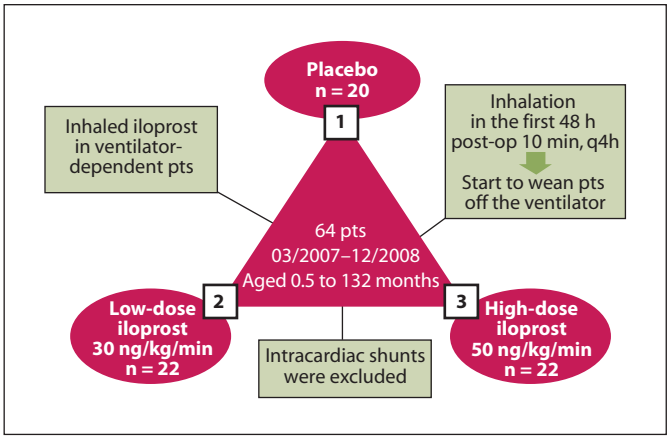

Fig. 5. Iloprost after paediatric congenital heart defect corrective surgery. Study design of a pilot study.

Results and Conclusion

Iloprost significantly reduced the mPAP, the pulmonary to systemic arterial pressure ratio (Pp/Ps), the transpulmonary gradient, the PVR index, and the pulmonary to systemic resistance ratio (Rp/Rs) in a dose-dependent manner, while the systemic vascular resistance index remained unchanged. The cardiac index rose significantly in the high-dose group (table 2).

One patient died in hospital; 8 patients developed pulmonary hypertensive crisis, 5 of them in the placebo group (7.8%), 2 in the low-dose iloprost group (3.1%) and only 1 in the high-dose iloprost group (1.6%).

This pilot study thus confirmed inhaled iloprost to be a selective pulmonary vasodilator that improved haemodynamics and prevented reactive PH and pulmonary hypertensive crises in mechanically ventilated children after CHD repair.

Table 2. Comparison of haemodynamics in the 3 study groups vs. baseline values

Parameters	Placebo group		Low-dose iloprost group		High-dose iloprost group	
	immediately after inhalation	30 min after inhalation	immediately after inhalation	30 min after inhalation	immediately after inhalation	30 min after inhalation
Mean pulmonary arterial pressure	+6.7%*	+6.9%*	−12.6%**	−11.3%*	−25.5%*	−23.7%*
Pulmonary to systemic arterial pressure ratio (Pp/Ps)	+5.2%*	+6.5%*	−32.0%*	−30.7%*	−42.7%*	−42.4%*
Pulmonary to systemic resistance ratio (Rp/Rs)	+7.1%*	+6.8%*	−18.1%*	−12.4%*	−22.1%*	−24.0%*
Transpulmonary gradient	+4.8%	+4.5%	−21.1%**	−14.0%*	−30.1%*	−28.4%*
Pulmonary vascular resistance index	+5.1%	+5.3%	−12.4%**	−13.7%*	−13.2%*	−16.8%*
Systemic vascular resistance index	+6.1%	+6.2%	−0.8%	−1.3%	−1.0%	−1.6%
Cardiac index	−0.3%	−0.3%	+15.1%	+15.5%	+18.4%*	+17.9%*

* $p < 0.05$; ** $p < 0.01$.

Plenary Discussion

Regarding the peri-operative management of high-risk children with CHD, Matthias Gorenflo, from Belgium, stated that he would prefer to perform combination therapy (iNO and inhaled iloprost), because 'it is well-known from the adults, that one substance is good, but two is probably better'.

Ralf Geiger, from Austria, said that in his hospital they do not see these critically ill patients any more. He himself worked with inhaled iloprost a lot, and he was the one who pushed this substance forward in his hospital, because he is convinced of the utility of this substance and of its efficacy in children with acute peri-operative or chronic PH. Mainly in chronic PH, problems may arise with maintaining correct and regular administration of the aerosol. Therefore, if a patient shows no or only a minor response, the administration modality should be checked first.

Tsvetomir Loukanov, from Germany, stated that his colleagues in China are obviously confronted with patients that are very rarely seen in his hospital, and so one must be very careful in defining the study groups, and in extrapolating the results. A placebo-controlled study in this severely ill Chinese patient group that showed significant results in favour of inhaled iloprost is of high value.

Matthias Gorenflo added that anaesthesiologists in his hospital prefer iNO because they think it is less complicated to use than iloprost. They are not afraid of the rebound phenomenon that can occur when the patient is weaned off iNO, because they use sildenafil to support the weaning process.

Theophani Antoniou, from Greece, stated that she uses inhaled iloprost and iNO in equal measure. Her experience is that iloprost is effective in serious situations such as in the peri-operative setting of heart transplant or valve replacement patients. She had also used iNO and inhaled iloprost in combination in 6 or 8 adult patients with very severe peri-operative hypertension. When the surgical procedure was started, the systolic pulmonary artery pressure in these adults was >100 mm Hg. Weaning off these patients from the cardiopulmonary bypass was successfully accomplished with a combination of the two inhalable substances (10–20 μg iloprost per inhalation plus 10 ppm iNO).

Matthias Gorenflo pointed out that in the Chinese studies CHD patients were treated surgically even when they presented with a PVR index of 11 Wood U or more. Most of his colleagues in Europe would not want to operate on patients with a PVR index above 6 or 8 Wood U.

Zhuoming Xu, from China, explained that in her hospital in Shanghai, preoperative vasoreactivity testing is performed on a regular basis in patients with borderline operability. However, the decision whether a congenital heart defect should be corrected or not ultimately depends on the decision of the surgeon, the patient, and the patient's family.

After the operation, the patients are followed up for one year. Right heart catheterization is not performed during follow-up for financial reasons. A big problem in China is the late referral of many patients. Therefore, after the operation, the pulmonary to systemic arterial pressure ratio (Pp/Ps) is virtually never below 0.5. Depending on the financial situation of the parents, children are treated with specific oral drugs such as bosentan or sildenafil during the follow up period and possibly thereafter.

Ralf Geiger, Austria, pointed out that he would not recommend operating on patients with Eisenmenger reaction, i.e. in patients with very high pulmonary vascular resistance and right-left-shunt. He would prefer to leave these Eisenmenger patients (or near-Eisenmenger patients) with late referral without surgical correction, because this probably leads to better long-term results and to better long-term survival than an operation followed by a PH-specific drug therapy.

Hong Gu said that she was trained at the Tokyo Women's Medical University, Japan. There, vasoreactivity tests are done on a regular basis, and the patient selection criterion for surgery is a 20% reduction in PVR index after inhalation of iloprost or a comparable vasodilator. Other centres use 10 or 30% reductions as the cut-off point. Concerning patients with a ventricular septal defect, surgical correction is recommended when the baseline PVR index is below 10 Wood U; in patients with an atrial septal defect, baseline PVR index should be below 14 Wood U.

Conflict of Interest

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References

1 Lindberg L, Olsson AK, Jögi P, et al: How common is severe pulmonary hypertension after pediatric cardiac surgery? J Thorac Cardiovasc Surg 2002;123:1155–1163.
2 Bizzarro M, Gross I: Inhaled nitric oxide for the postoperative management of pulmonary hypertension in infants and children with congenital heart disease. Cochrane Database Syst Rev 2005;CD005055.
3 Miller OI, Tang SF, Keech A, et al: Inhaled nitric oxide and prevention of pulmonary hypertension after congenital heart surgery: a randomised double-blind study. Lancet 2000;356:1464–1469.
4 Macrae DJ, Field D, Mercier JC, et al: Inhaled nitric oxide therapy in neonates and children: reaching a European consensus. Intensive Care Med 2004;30:372–380.
5 Ivy DD, Doran AK, Smith KJ, et al: Short- and long-term effects of inhaled iloprost therapy in children with pulmonary arterial hypertension. J Am Coll Cardiol 2008;51:161–169.
6 Limsuwan A, Wanitkul S, Khosithset A, et al: Aerosolized iloprost for postoperative pulmonary hypertensive crisis in children with congenital heart disease. Int J Cardiol 2008;129:333–338.
7 Hallioglu O, Dilber E, Celiker A, et al: Comparison of acute hemodynamic effects of aerosolized and intravenous iloprost in secondary pulmonary hypertension in children with congenital heart disease. Am J Cardiol 2003;92:1007–1009.
8 Beghetti M, Tissot C: Pulmonary arterial hypertension in congenital heart diseases. Semin Respir Crit Care Med 2009;30:421–428.
9 Ma M, Gauvreau K, Allan CK, et al: Causes of death after congenital heart surgery. Ann Thorac Surg 2007;83:1438–1445.
10 Rimensberger PC, Spahr-Schopfer I, Berner M, et al: Inhaled nitric oxide versus aerosolized iloprost in secondary pulmonary hypertension in children with congenital heart disease: vasodilator capacity and cellular mechanisms. Circulation 2001;103:544–548.