Comparison of Acute Hemodynamic Effects of Aerosolized Iloprost and Inhaled Nitric Oxide in Adult Congenital Heart Disease with Severe Pulmonary Arterial Hypertension

Zhang Caojin, Huang Yigao, Huang Tao, Huang Wenhui, Xia Chunli and Huang Xinsheng

Abstract

Objective To compare the acute hemodynamic effects of aerosolized iloprost and inhaled nitric oxide (NO) in adult congenital heart disease (CHD) patients with severe pulmonary arterial hypertension (PAH).

Methods One hundred and eighty five adult CHDs with severe PAH were nonrandomized into two groups (iloprost, n=127; NO, n=58). Various hemodynamic parameters were measured before and after iloprost or NO inhalation.

Results Iloprost and NO inhalation resulted in significant reductions in pulmonary arterial pressure (from 110.6±21.8 mmHg to 105.5±22.3 mmHg, p<0.05; from 113.1±18.7 mmHg to 107.2±19.9 mmHg, p<0.05, respectively) and pulmonary vascular resistance (PVR) (from 13.4±8.3 Wood units to 9.6±6.4 Wood units, p<0.01; from 13.7±7.1 Wood units to 9.3±4.9 Wood units, p<0.01, respectively) and increases in pulmonary blood flow (from 6.7±3.3 L/min to 9.4±5.8 L/min, p<0.05; from 6.6±3.1 L/min to 9.6±5.9 L/min, p<0.01, respectively) and the Qp/Qs ratio (from 1.5±0.8 to 2.1±1.4, p<0.01; from 1.5±0.8 to 2.0±1.3, p<0.01, respectively). When the effects of inhaled iloprost and NO were compared, similar reductions in pulmonary arterial pressure and pulmonary vascular resistance were observed. Aerosolized iloprost and inhaled nitric oxide (iNO) were generally well tolerated and no patient experienced any side effects during inhalation.

Conclusion Aerosolized iloprost can be effectively and safely used and might be an alternative to NO for testing pulmonary vascular reactivity and treating severe PAH in adult CHD patients.

Key words: pulmonary arterial hypertension, congenital heart disease, pulmonary vascular resistance, iloprost

(DOI: 10.2169/internalmedicine.51.7927)

Introduction

Pulmonary arterial hypertension (PAH) associated with congenital heart disease (CHD) is one of the most common causes of severe morbidity and premature mortality in patients with CHD. The assessment of pulmonary vascular reactivity plays an important role in the management of these patients. The reversibility of PAH should be tested with various vasodilators. Currently, three short-acting agents are widely recommended in the guidelines for acute pulmonary vasoreactivity testing: intravenous (i.v.) epoprostenol, i.v. adenosine and inhaled nitric oxide (iNO). The agent most frequently used in acute testing is NO (1, 2). However, the administration of iNO is complicated and requires complex monitoring devices, and acute withdrawal of iNO can lead to dangerous rebound pulmonary hypertension (3, 4). The inhalation of aerosolized iloprost, a long-acting prostacyclin analogue, may be associated with significant vasodilator effects (1, 2). Based on previous experience, iloprost causes strong preferential pulmonary vasodilatation in both primary and secondary pulmonary hypertension (5-7). The long-term use of nebulized iloprost has been shown to be beneficial in treating severe primary pulmonary hypertension and overt right-heart failure (8-10). Furthermore, inhaled iloprost requires no specific monitoring and is less expensive. However, there is little information on the use of iloprost in adult patients with PAH secondary to CHD. The aim of the pre-
sent study was to investigate the acute hemodynamic effects of inhaled aerosolized iloprost in adult patients with severe PAH associated with CHD.

### Materials and Methods

#### Study population

Between February 2005 and July 2011, 185 adult patients were enrolled in the present study. The study population comprised adults with severe PAH secondary to CHD. Severe PAH was defined as a systolic pulmonary artery pressure (PAP) greater than two-thirds of the systemic level (11, 12). At catheterization, those found to have either pulmonary vascular resistance (PVR) or PVR >5 Wood units (12). This study was approved by the Institutional Ethics Committee at Guangdong General Hospital. Written informed consent was obtained from all patients prior to enrollment.

#### Hemodynamic assessment

In each patient, appropriately sized introducer sheaths were placed into both the femoral vein and femoral artery under local anesthesia. The catheter was inserted into a femoral vein and placed in the superior vena cava, the inferior vena cava, the pulmonary artery, the left atrium and the aorta to allow simultaneous measurement of pressure and blood gases and to avoid time-consuming and confounding measurements due to catheter manipulations. In patients with atrial septal defects or patent foramen ovales, catheters were placed in a pulmonary vein instead of the left atrium. In the absence of an interatrial communication, the pulmonary capillary wedge pressure (PCWP) was measured instead of the left atrial pressure. Intravascular pressures were measured with fluid-filled transducers, and the oxygen content was calculated from hemoglobin concentrations and oxygen saturations. The cardiac index, pulmonary and systemic blood flow (Qp and Qs, respectively) calculations based on the Fick principle (13) were obtained from assumed oxygen consumption. PVR and SVR were calculated with standard formulas and indexed to body surface area.

After baseline values were obtained, patients were non-randomized into two groups (iloprost or NO). In the iloprost group, aerosolized iloprost was administered at a dose of 20 μg diluted in 2 mL of isotonic saline solution and nebulized for 10 minutes by way of the MicroDrop Master Jet (MPV, Truma, Germany) using a particle size of 3 μm to provide alveolar deposition of the substance. In the iNO group, iNO was administered at a dose of 20 parts per million (ppm) using a commercially available system for iNO application and concentration measurement. The administered dose and nebulization time of iloprost were in agreement with the references (14, 15). Hemodynamic parameters were measured at baseline and at the end of inhalation of aerosolized iloprost or NO.

#### Statistical analysis

The data are expressed as the mean ± the SD. Differences in the hemodynamic parameters before and after intervention were assessed via the paired samples t-test. Differences in parameters between groups were compared using the unpaired samples t-test. The statistical analyses were performed with the SAS 8.1 software package. A p value <0.05 was considered to be statistically significant.

### Results

A total of 185 adult congenital heart disease patients (122 women and 63 men) with severe PAH were enrolled in this study. The average patient age was 31±10 years (range: 18-72 years). The diagnoses included 77 cases of atrial septal defects (ASD), 62 cases of ventricular septal defects (VSD), 31 cases of patent ductus arteriosus (PDA) and 15 cases of complex congenital heart diseases. The iNO group included 58 cases and the iloprost group included 127 cases. The baseline data are shown in Table 1.

NO was administered to determine the pulmonary vascular reactivity between February 2005 and December 2006, and iloprost was administered between January 2007 and July 2011. The hemodynamic parameters measured at baseline and at the end of inhalation of iloprost (n=127) or NO (n=58) are listed in Table 2. No significant differences in the hemodynamic parameters were noted between the two groups at baseline. Iloprost and NO inhalation resulted in significant reductions in pulmonary arterial pressure (from 110.6±21.8 mmHg to 105.5±22.3 mmHg, p<0.05; from
Table 2. The Comparison of Hemodynamic Data in Patients with Severe Pulmonary Hypertension at Baseline and after Inhalation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>After inhalation</th>
<th>Amplitude of variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>89±18</td>
<td>87±19</td>
<td>87±17</td>
</tr>
<tr>
<td>PAP(mmHg)</td>
<td>113.1±18.7</td>
<td>107.2±19.9*</td>
<td>-5.8±12.3</td>
</tr>
<tr>
<td>PAPd(mmHg)</td>
<td>46.7±15.9</td>
<td>42.6±15.1</td>
<td>-4.8±11.8</td>
</tr>
<tr>
<td>PAPm(mmHg)</td>
<td>72.2±16.8</td>
<td>67.2±16.2*</td>
<td>-5.6±16.1</td>
</tr>
<tr>
<td>PCWP(mmHg)</td>
<td>11.5±4.2</td>
<td>11.7±4.1</td>
<td>0.2±0.7</td>
</tr>
<tr>
<td>APA(mmHg)</td>
<td>121.3±16.8</td>
<td>115.6±17.9*</td>
<td>-5.3±9.6</td>
</tr>
<tr>
<td>APA(mmHg)</td>
<td>72±11</td>
<td>69.2±11.2</td>
<td>-2.7±8.8</td>
</tr>
<tr>
<td>APA(mmHg)</td>
<td>90.6±12.1</td>
<td>87.9±13.1</td>
<td>-3.7±6.4</td>
</tr>
<tr>
<td>RAm(mmHg)</td>
<td>6.6±3.7</td>
<td>7.5±2.9</td>
<td>0.9±0.8</td>
</tr>
<tr>
<td>Pp/Ps</td>
<td>0.92±0.17</td>
<td>0.91±0.19</td>
<td>-0.004±0.09</td>
</tr>
<tr>
<td>Qt(L/min)</td>
<td>6.6±3.1</td>
<td>9.5±6.59**</td>
<td>3±5.8</td>
</tr>
<tr>
<td>Qs(L/min)</td>
<td>4.8±1.3</td>
<td>5±1.4</td>
<td>0.3±1.4</td>
</tr>
<tr>
<td>CI(L/min/m²)</td>
<td>3.35±0.7</td>
<td>3.5±0.6</td>
<td>0.15±0.5</td>
</tr>
<tr>
<td>Qp/Qs</td>
<td>1.5±0.8</td>
<td>2±1.3**</td>
<td>0.5±0.9</td>
</tr>
<tr>
<td>PVR(Wood unit)</td>
<td>13.7±7.1</td>
<td>9.3±4.9**</td>
<td>-4.5±3.9</td>
</tr>
<tr>
<td>SVR(Wood unit)</td>
<td>18.2±5.3</td>
<td>17±5.1</td>
<td>-0.9±5.5</td>
</tr>
<tr>
<td>L-to-R shunt(L/min)</td>
<td>2.8±2.9</td>
<td>5.2±5.8**</td>
<td>2.4±3.3</td>
</tr>
<tr>
<td>R-to-L shunt(L/min)</td>
<td>1.0±0.7</td>
<td>0.7±0.6**</td>
<td>-0.3±0.8</td>
</tr>
</tbody>
</table>

113.1±18.7 mmHg to 107.2±19.9 mmHg, p<0.05, respectively) and PVR (from 13.4±8.3 Wood units to 9.6±6.4 Wood units, p<0.01; from 13.7±7.1 Wood units to 9.3±6.4 Wood units, p<0.01, respectively) and in increases in pulmonary blood flow (from 6.7±3.3 L/min to 9.4±5.8 L/min, p<0.05; from 6.6±3.1 L/min to 9.6±5.9 L/min, p<0.01, respectively) and the Qp/Qs ratio (from 1.5±0.8 to 2.1±1.4, p<0.01; from 1.5±0.8 to 2.0±1.3, p<0.01, respectively). As shown in Table 1, the femoral arterial blood oxygen saturation (SaO2), pulmonary arterial blood oxygen saturation (PaO2), and mixed venous blood oxygen saturation (SvO2) levels were markedly increased following intervention compared to those at baseline in both groups (p<0.01). Furthermore, the magnitude of the increase in SvO2 in the iloprost group was greater than that in the NO group (7.5±5.9% vs. 5.4±6.3%; p<0.05). Neither agent showed significant effects on systemic blood flow or SVR. More importantly, when the effects of inhaled iloprost and iNO were compared, similar reductions in the pulmonary arterial pressure and PVR were observed.

In the iloprost group, iloprost caused decreases in pulmonary arterial pressure (PAP) in 99 patients and slight increases in systolic pulmonary arterial pressure in 28 patients. The mean systemic aortic pressure decreased from 121.1±18.8 mmHg to 116.7±19.5 mmHg (p<0.05) with aerosolized iloprost application; however, the mean aortic pressure did not significantly change. Aerosolized iloprost increased left-to-right shunting (from 3.1±2.9 L/min to 5.2±5.6 L/min, p<0.01) and decreased right-to-left shunting (from 0.9±0.8 L/min to 0.6±0.7 L/min, p<0.01). In the NO group, overall decreases in PAP and PVR were observed after NO inhalation. NO also caused increases in pulmonary blood flow and Qp/Qs ratios, especially in left-to-right shunts (from 2.8±2.9 L/min to 5.2±5.8 L/min, p<0.01). Aerosolized iloprost and NO were generally well tolerated and no patient experienced any side effects during inhalation.

**Discussion**

Pulmonary arterial hypertension complicates the clinical
courses of many adult patients with CHD. Increases in PAH associated with CHD are secondary to either increased pulmonary blood flow or increased postcapillary pressure. The recent introduction of targeted therapies for other forms of PAH (1, 2) has led to a renewed interest in PAH associated with CHD and in Eisenmenger syndrome in particular. Inhaled therapy for PAH is an attractive concept that has the theoretical advantage of being selective for pulmonary circulation. Iloprost is a carboxyclic analogue of PGI2 that has a plasma half-life of 20 to 30 minutes (16). When inhaled, iloprost seems to cause preferential pulmonary vasodilation that lasts for approximately one to two hours (7). Olschewski et al. first described the use of aerosolized iloprost for treating severe pulmonary hypertension (7). Since then, several studies have demonstrated that short-term aerosolized iloprost elicits favorable effects on pulmonary hemodynamics without significantly decreasing systemic blood pressure in adult patients with primary pulmonary hypertension (8-10, 17). The use of inhaled iloprost has also been evaluated in some RCTs (18-21), with the results showing increases in exercise capacity and improvements in symptoms, PVR and clinical events in enrolled patients. Few published reports specifically describe the acute hemodynamic effects of aerosolized iloprost in adults with pulmonary hypertension secondary to CHD (22, 23). In comparison, in our study, we found similar effects of inhaled aerosolized iloprost in adult patients with severe PAH due to CHD. In this study, iloprost inhalation caused significant reductions in pulmonary arterial pressure and PVR. The Pp/Ps ratio and SVR were not markedly changed and the Rp/Rs ratio was decreased following iloprost inhalation. Therefore, iloprost may cause selective decreases in PVR. In addition to exerting beneficial effects on the pulmonary vascular bed, iloprost caused significant increases in pulmonary blood flow.

The ideal drug to assess acute vasoreactivity should be potent, titratable, short-acting and convenient to administer. It should also be widely available, making cost an important criterion as well. Intravenous epoprostenol and adenosine and iNO are the most widely used and extensively studied agents (1) and are recommended by current guidelines (1, 2); however, none of these drugs fully satisfy all of the aforementioned criteria. While iNO is the optimum drug with respect to pulmonary selectivity, ease of administration and pharmacological profile, it is expensive and requires dedicated and costly technical equipment, making it impractical for use outside of specialty centers in industrialized countries. Iloprost might have some advantages over the inhalation of NO, including its lack of toxic reactions (24, 25) (iNO requires monitoring of NO2 and methemoglobin formation during NO inhalation) and ease of administration using conventional nebulizers compared with the more complicated delivery systems required for NO. The more potent acute effects of iloprost on PVR are reflected not only by more apparent declines in pulmonary arterial pressure, but also by more prominent increases in systemic blood flow. The direct positive inotropic action of iloprost could be an alternative explanation because prostanoid-mediated increases in cyclic AMP (cAMP) in cardiomyocytes have been shown to exert positive inotropic effects in experimental models (26, 27). Peter et al. (28) reported that iNO increases cyclic GMP (cGMP) and iloprost increases cAMP in children with PAH and CHD and that both iNO and aerosolized iloprost are equally effective in selectively lowering PVR through increases in cGMP and cAMP, respectively. The present study demonstrates that inhaled iloprost and NO are equally effective in reducing pulmonary arterial pressure and PVR and increasing pulmonary blood flow and the Qp/Qs ratio. An additional finding of this study is that, in adult patients with CHD and severe PAH, inhaled iloprost and NO can immediately improve pulmonary hemodynamics and oxygenation. In particular, in this study, the magnitude of the increase in SvO2 in the iloprost group was higher than that in the NO group. Considering the findings of this comparison study and the prior reports noted above, there is now growing evidence for the use of inhaled iloprost as an alternative agent to NO in the assessment of pulmonary vascular reactivity and reversibility of PAH in adult CHD patients. Inhaled iloprost exerts selective pulmonary vasodilative effects and is beneficial for pulmonary gas exchange. Therefore, aerosolized iloprost might be an alternative to iNO in the early testing of vascular reactivity and also for the treatment of severe PAH in adult CHD patients.

It is of utmost importance to identify the hemodynamic cause of PAH in the setting of CHD. In CHD with left-to-right shunting, increases in mean pulmonary arterial pressure may be due to either or both increases in pulmonary blood flow and/or increases in PVR. The acute effects of inhaled iloprost on pulmonary hemodynamics are reflected not only by more pronounced declines in pulmonary arterial pressure, but also by prominent increases in the pulmonary-to-systemic flow ratio. In our study, inhaled iloprost caused slightly increases in systolic pulmonary arterial pressure in 28 patients. This may have been due to decreases in PVR and increases in pulmonary blood flow, which can result in increases in systolic pulmonary arterial pressure. This result showed that iloprost may selectively relax the pulmonary vessels.

However, declines in systemic blood pressure are a potential side effect in patients receiving PGI2 and its carboxyclic analogue, and some patients with advanced right heart failure may not tolerate even the lowest doses of PGI2 (29). We observed no changes in systemic vascular resistance or in systemic arterial pressure during iloprost inhalation such as those reported by other investigators (5).

In the present study, the subjects were limited to adult CHD patients. The selectivity of aerosolized iloprost for pulmonary circulation was achieved: pulmonary arterial pressure and PVR decreased, pulmonary blood flow and the Qp/Qs ratio increased and systemic blood pressure remained stable. Aerosolized iloprost—at least at the doses used in our study—is significantly more potent in reducing pulmonary arterial pressure and PVR and also causes significantly
greater increases in pulmonary blood flow. Moreover, in this study, aerosolized iloprost was well tolerated and no major side effects were observed. Therefore, aerosolized iloprost can be effectively and safely used and has the potential to become a valuable new choice for acute vasoreactivity testing in adult patients with severe PAH secondary to CHD. However, there are several limitations to this study: a) There were many confounding variables that may have affected the oxygenation and hemodynamic parameters such as assumed oxygen consumption, organ function and so on. b) The number of studied subjects in the NO group was markedly less than that in the iloprost group. c) With the nebulizer method of drug delivery, the exact amount of aerosolized iloprost that reaches the alveoli is uncertain because of losses in the nebulizer chamber.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement
This work was supported by the Science and Technology Foundation of Guangdong Province (No. 2008B030301168).

References