Efficacy of Acute Inhalation of Nitric Oxide in Patients With Primary Pulmonary Hypertension Using Chronic Use of Continuous Epoprostenol Infusion

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Background There have only been a few reports published on combination therapy for patients with primary pulmonary hypertension (PPH).

Methods and Results Fifteen patients with PPH (4 men and 11 women; 34.5±12.1 years old) had received chronic administration of epoprostenol and the additive effects of inhaled nitric oxide (NO) and the hemodynamic changes were evaluated. In addition, the difference in the effect of acute NO loading before and after the epoprostenol therapy was compared in 6 of these patients. Under chronic use of epoprostenol, mean pulmonary arterial pressure, mean right atrial pressure and pulmonary vascular resistance were decreased with acute inhalation of NO. However, cardiac output, mean aortic pressure and systemic vascular resistance were unchanged. As a result, the pulmonary to systemic vascular resistance ratio was reduced. Moreover, after chronic use of epoprostenol, the change (delta) in cardiac output with NO inhalation was increased and the NO-induced decrease in pulmonary vascular resistance was augmented compared to those before the induction.

Conclusion Nitric oxide inhalation further improved the hemodynamics when combined with chronic use of epoprostenol in PPH patients. These results suggest the possibility that combination therapies can be used in the treatment for PPH patients. (Circ J 2005; 69: 335–338)

Key Words: Epoprostenol; Fractional pulse pressure; Nitric oxide; Pulmonary angiography; Pulmonary arterial hypertension

Primary pulmonary hypertension (PPH), considered to be a disease with a very poor prognosis, is characterized by advanced pulmonary hypertension of unexplained etiology and right heart failure. Recently, mutations in the bone morphogenetic protein receptor 2 gene have been identified in cases of familial and sporadic PPH. Although chronic use of epoprostenol has been used to improve the patients’ quality of life, New York Heart Association (NYHA) functional class and the prognosis of PPH patients, deem such treatment as still insufficient. The validity of combination therapy for pulmonary hypertension has been demonstrated in some animal models. However, it is difficult to prove the clinical efficacy of such therapy in human.

In the current study, we investigated the clinical possibility of combination therapy by evaluating the acute additional effect of nitric oxide (NO) inhalation on the pulmonary blood vessels in PPH patients under chronic treatment with epoprostenol.

Methods Fifteen patients with PPH (4 men and 11 women; 34.5±12.1 years old, ranging from 18 to 53) participated in the present study. Patients with secondary pulmonary hypertension, including pulmonary embolism, collagen pulmonary hypertension, portopulmonary hypertension, Eisenmenger syndrome and post-capillary pulmonary hypertension were carefully excluded using imaging techniques, cardiac catheterization, echocardiography, lung scintigraphy, abdominal ultrasound, computer tomography and laboratory tests. Cardiac catheterization was carried out before administering epoprostenol and during the chronic epoprostenol use (20.1±16.5 months). Measured hemodynamic indices were the following: pulmonary capillary wedge pressure, pulmonary arterial pressure, right ventricular pressure, right atrial pressure, aortic pressure and cardiac output. The mean dose of epoprostenol in the chronic phase was 32.1±13.8 ng·kg⁻¹·min⁻¹ (range: 8.5–52.4 ng·kg⁻¹·min⁻¹). The same hemodynamic indices were measured after 10min inhalation of NO (40ppm) at the time of right heart catheterization in the chronic phase. In 6 of these patients (6 women; 38.7±10.1 years old), the difference in the effect of acute NO loading before and after the epoprostenol therapy was evaluated. Fractional pulse pressure was calculated as pulmonary pulse pressure divided by mean pulmonary artery pressure. In 5 patients, wedged pulmonary angiography was carried out both before and after administering epoprostenol without NO.
inhalation. Inhaled NO was approved by the Ethics Committee of Tohoku University. All patients signed informed consent forms.

Statistics
Comparisons between 2 groups were evaluated by Wilcoxon signed-ranks test, and multiple comparisons were analyzed by Bonferroni correction using StatView5.0 (SAS Institute Inc). A correlation between 2 parameters was obtained by Spearman’s rank correlation. Data are given as mean±standard deviation. All reported p-values are 2-tailed.

Results
Acute inhalation of NO significantly decreased the mean pulmonary arterial pressure, mean right atrial pressure and pulmonary vascular resistance under the chronic use of epoprostenol. No significant differences were observed in cardiac output or mean arterial pressure. Moreover, there was no significant reduction in systemic vascular resistance. Consequently, a significant decline in the pulmonary to systemic vascular resistance ratio was observed (Table 1). Fractional pulse pressure was reduced 0.87±0.13 (range: 0.49–1.02) to 0.82±0.12 (range: 0.55–0.98) but not significant (p=0.088). There was a loose positive correlation between percentage change of pulmonary vascular resistance by chronic use of epoprostenol and further percentage change in NO inhalation (r=0.32, Fig 1).

In addition, after chronic use of epoprostenol, the change (delta) in cardiac output by NO inhalation was increased. The NO-induced decrease in pulmonary vascular resistance was augmented compared to that before epoprostenol induction (Table 2).

Wedged pulmonary angiography showed that the small pulmonary artery was dilated and more peripheral vessels, recognized by their cotton-like appearance, increased after chronic use of epoprostenol in all 5 cases examined by angiography (Fig 2).

Discussion
Epoprostenol has opened a new era in the treatment for pulmonary arterial hypertension. Subsequently, epoprostenol analog (beraprost, iloprost), endothelin receptor antagonist (bosentan), phosphodiesterase-V inhibitor (sildenafil) and NO inhalation have been tried and shown to have certain effects.9–23 Thus, therapeutic choices with new medicines have been increasing. However, combined therapy might provide another choice.

In the present study, NO inhalation decreased the mean pulmonary arterial pressure and pulmonary vascular resistance when combined with the chronic use of epoprostenol in all 5 cases examined by angiography (Fig 2).

Table 1 Acute Effects of NO Inhalation on Hemodynamics With Chronic Use of PGI2 (n=15)

<table>
<thead>
<tr>
<th></th>
<th>Base</th>
<th>Chronic PGI2</th>
<th>Chronic PGI2: + acute NO</th>
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<tbody>
<tr>
<td>HR (beats/min)</td>
<td>81±12</td>
<td>86±15</td>
<td>86±14</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>8.8±4.6</td>
<td>9.4±2.1</td>
<td>9.1±2.6</td>
</tr>
<tr>
<td>PAP (mmHg)</td>
<td>71±14</td>
<td>54±19**</td>
<td>51±19**</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>10.1±5.9</td>
<td>8.1±4.2</td>
<td>6.9±3.8*</td>
</tr>
<tr>
<td>AoP (mmHg)</td>
<td>85±12</td>
<td>84±15</td>
<td>85±11</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>3.11±0.69</td>
<td>4.71±1.12**</td>
<td>5.00±0.98</td>
</tr>
<tr>
<td>PVR (dyn·s·cm−5)</td>
<td>1.66±0.47</td>
<td>860±535**</td>
<td>722±436**</td>
</tr>
<tr>
<td>SVR (dyn·s·cm−5)</td>
<td>1.997±0.36</td>
<td>1.379±0.42**</td>
<td>1.307±0.35</td>
</tr>
<tr>
<td>PVR/SVR</td>
<td>0.86±0.22</td>
<td>0.59±0.22**</td>
<td>0.54±0.22**</td>
</tr>
</tbody>
</table>

*p<0.05 and **p<0.01 vs previous condition. All variables are shown as mean±standard deviation.

NO, nitric oxide; PGI2, epoprostenol; HR, heart rate; PCWP, pulmonary capillary wedge pressure; PAP, mean pulmonary artery pressure; RAP, mean right atrial pressure; AoP, mean aortic pressure; CO, cardiac output; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

Table 2 Changes (Delta) in Acute Effects of NO Inhalation on Hemodynamics After Chronic Use of PGI2 (n=6)

<table>
<thead>
<tr>
<th></th>
<th>Before PGI2 use</th>
<th>After PGI2 use</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>–3±2 (–3±4%)</td>
<td>2±4* (2±6%)</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>–0.2±1.2 (5±31%)</td>
<td>–0.3±0.8 (–3±12%)</td>
</tr>
<tr>
<td>PAP (mmHg)</td>
<td>–4±4 (–6±5%)</td>
<td>–3±4 (–7±10%)</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>–1.2±1.5 (–20±14%)</td>
<td>–0.8±1.2 (–9±17%)</td>
</tr>
<tr>
<td>AoP (mmHg)</td>
<td>–3±2 (2±3%)</td>
<td>1±6 (2±7%)</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>–0.2±0.6 (–3±20%)</td>
<td>0.0±0.5* (15±11%)</td>
</tr>
<tr>
<td>PVR (dyn·s·cm−5)</td>
<td>–4±473 (12±25%)</td>
<td>–147±70 (–19±11%)*</td>
</tr>
<tr>
<td>SVR (dyn·s·cm−5)</td>
<td>105±368 (9±19%)</td>
<td>–124±164 (–9±12%)</td>
</tr>
<tr>
<td>PVR/SVR</td>
<td>–0.06±0.07 (–8±9%)</td>
<td>–0.05±0.06 (–10±14%)</td>
</tr>
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</table>

*p<0.05. See Table 1 for abbreviations.
method.

The first method in the studies on combination therapy for PPH was to assess the combined effect by acute loading of 2 medicines. Wilkens et al reported the effect of acute loading of oral administration of sildenafil and inhalation of iloprost in PPH patients. They showed that the mean pulmonary arterial pressure was significantly decreased with this combination therapy compared with either drug alone. However, under this condition, it is unclear whether one medicine was effective after the other had been given adequately.

The second method was to elucidate the combined effect of 2 medicines given simultaneously and chronically. This method is the most reliable if it is applied to randomized tests. However, it is relatively difficult to evaluate the effects in clinical settings. Ueno et al examined the chronic effect of a combination therapy (endothelin-A receptor antagonist and beraprost sodium), in monocrotalin-induced pulmonary hypertension rats. They showed that the combination therapy was much more effective in improving the pulmonary to systemic vascular resistance ratio than each medicine used alone. In pulmonary hypertension rats treated with combination therapy, the decrease in the ratio of the minor axis to the major axis of the left ventricle in the end-systolic phase, and the increase in the wall thickness of pulmonary blood vessels and right ventricular weight/body weight ratio were restored compared to those of pulmonary hypertension rats with either medicine alone.

The third method was to assess the chronic additional effect of other medicines after chronic administration of one medicine. Ghofrani et al added sildenafil chronically to the patients for whom prolonged administration of iloprost had not been effective. In that study, the pulmonary vascular resistance and 6 min walk test were significantly improved. Their cases were limited to those for which the first medicine was ineffective, and the evaluation of the additional medicine was not conducted when the first medicine was effective.

These studies mentioned above, including our study, tried to assess the efficacy of a combination therapy using 2 or more medical agents with different mechanisms to dilate the vessels. For example, as for the combination of epoprostenol and NO used in the present study, epoprostenol dilated the vessels through cyclic adenosine monophosphate (cAMP), and NO mainly through cyclic guanosine monophosphate (cGMP) and partially through cAMP. This may indicate that sufficient pulmonary vasodilation might not be obtained with a single medicine. In patients with serious systemic hypertension, combination therapy for the disease is commonly used. Therefore, it would seem reasonable to use combination therapy for pulmonary arterial hypertension.

In addition, we also assessed the reactivity to NO in patients with PPH for whom NO inhalation had not been effective in improving the hemodynamics in the beginning. After the chronic administration of epoprostenol, NO inhalation resulted in a significant increase in the cardiac index and a decrease in the total pulmonary vascular resistance in all 7 patients.

It is well-known that epoprostenol reduces pulmonary vascular resistance in chronic use, but the mechanism has not been determined. Fig 1 indicates that the NO-induced additive decrease in pulmonary vascular resistance tended to be larger in cases with larger reductions in pulmonary vascular resistance by chronic use of epoprostenol. This may mean that cases with more improvement in pulmonary vascular resistance by chronic use of epoprostenol have a greater reserve ability for pulmonary arterial dilation. Contrary to our expectations, the fractional pulse pressure, which has a higher value in the proximal pulmonary artery lesion, tended to decrease after epoprostenol therapy. Therefore, the lesion in the proximal pulmonary artery might improve more than in the peripheral vessels. Moreover, wedged pulmonary angiography showed that visible small pulmonary arteries dilated, and that more peripheral vessels, recognized by their cotton-like appearance, increased after chronic use of epoprostenol. These morphological changes in pulmonary arteries may ameliorate the pulmonary hypertension in part.
to be insufficient), and the best combination of medicines for the disease must also be clarified.

Clinical Implication
The present data indicate that inhaled NO may be useful in the acute deterioration of patients chronically using epoprostenol, or in cases early after using epoprostenol and for whom the effect of epoprostenol has not been sufficient. Nitric oxide donors and phosphodiesterase inhibitor V (sildenafil) also increase intra-cellular CGMP like inhaled NO. Inhaled NO was superior to these medicines in vascular selectivity and ventilation-perfusion matching, but inferior in convenience.

Conclusion
Nitric oxide inhalation showed further improvement of hemodynamics under chronic administration of epoprostenol in PPH patients. These results suggest the efficacy of combination therapy in PPH patients.

References