Hemodynamic Effects of Inhaled Nitric Oxide Using Pulse Delivery and Continuous Delivery Systems in Pulmonary Hypertension

Osamu Kitamukai, Masahito Sakuma, Tohru Takahashi, Jun Nawata, Jun Ikeda and Kunio Shirato

Abstract

Objective Inhaled nitric oxide (NO) has been used for pulmonary vasodilation therapy in patients with pulmonary hypertension. Inhaled NO for awake and ambulatory patients, however, is unusual because it requires intubation or a tightly fitting facemask, and a large-scale delivery system for the safe management of toxic nitrogen oxides. We undertook this study to investigate the possibility of using inhaled NO therapy for awake and ambulatory patients with pulmonary hypertension.

Methods Patients with pulmonary hypertension underwent cardiac catheterization and hemodynamic variables were measured at the baseline, after inhaled NO using our pulse delivery system, which involved a nasal cannula and a pulse device, and after inhaled NO using a continuous delivery system.

Patients or materials We studied seventeen patients with precapillary pulmonary hypertension (4 men and 13 women; age, 41±3, ranging from 19 to 61).

Results Cardiac output was increased significantly by each system. Pulmonary vascular resistance was decreased significantly by each system. There was no significant change in mean pulmonary artery pressure, mean systemic artery pressure, or systemic vascular resistance. The concentrations of NO and nitrogen dioxide (NO₂) in the expiratory gas using the pulse delivery system were 0.0 ppm as long as the pulse device was synchronized with the patient's respiratory cycle.

Conclusion Inhaled NO using our pulse delivery system changed the hemodynamic variables similarly to those when using the continuous delivery system. The concentrations of NO and NO₂ in the expiratory gas using the pulse delivery system were within safe limits.

Key words: vasodilation, primary pulmonary hypertension, pulmonary embolism, rheumatic disease, porto-pulmonary hypertension

Introduction

Inhaled nitric oxide (NO) is a selective pulmonary vasodilator (1). Its effect is considered ideal for the therapy of patients with pulmonary hypertension because, theoretically, it does not influence the systemic arterial pressure. There have been many reports describing the use of inhaled NO in cases with various causes of pulmonary hypertension (2-22). However, the clinical application of inhaled NO is restricted to short-term use and requires a delivery system consisting of a closed circuit with a scavenging system. Moreover, the use of inhaled NO requires monitoring of the concentrations of inhaled and environmental NO and nitrogen dioxide (NO₂) because it causes the formation of toxic NO₂ (23-26). Thus, in most cases, inhaled NO has been used for mechanically ventilated patients but has been considered difficult for awake and ambulatory patients who need long-term pulmonary vasodilation therapy to undergo inhaled NO therapy.

We undertook this study to investigate the possibility of using inhaled NO therapy for awake and ambulatory patients with pulmonary hypertension. In the present study, we lowered the concentration of inhaled NO and the concentrations of NO and NO₂ in the expiratory gas using a pulse delivery system and compared the hemodynamic effects of the pulse delivery system with those of a continuous delivery system.

Methods

Patients

We studied seventeen consecutive patients (4 men and 13 women; age, 41±3, ranging from 19 to 61) who underwent cardiac catheterization for diagnosis or for the estimation of therapy for precapillary pulmonary hypertension at our hospital between July 1999 and July 2000. Precapillary pulmonary hypertension was defined as a mean pulmonary artery pressure over 25 mmHg and a pulmonary capillary wedge pressure below 12 mmHg. The causes of precapillary pulmonary hypertension were primary pulmonary hypertension in 8 patients, chronic pulmonary thromboembolism in 5 patients, rheumatic
disease with pulmonary hypertension in 3 patients, and portopulmonary hypertension in one patient. The patient’s characteristics are shown in Table 1.

**NO delivery system**

In the pulse delivery system (Fig. 1), 100 ppm NO was delivered by a nasal cannula using a pulse device (sansosaver 2, TEIJIN, Tokyo) that is generally used in home oxygen therapy for patients with chronic obstructive pulmonary disease. The onset and duration of each pulse was automatically controlled to become activated during the first third of the inspiration time as predicted from the previous 3 respiratory cycles. The flow rate was fixed at 1.0 l/min. The nasal cannula had a double lumen, and the NO and oxygen were delivered separately to the end of the cannula. Expiratory gas was collected by a tightly fitting facemask and monitored for the concentrations of NO and NO\textsubscript{2} by an electrochemical analyzer (TMS-100, Taiyo-Toyo Sanso, Osaka).

In the continuous delivery system (Fig. 2), NO gas was delivered through a one-way inspiratory valve by a tightly fitting facemask. The concentration of inhaled NO was regulated by changing the flow of 1,000 ppm NO, that was blended with oxygen using a mass flow controller. The concentration of inhaled NO and NO\textsubscript{2} were monitored by an electrochemical ana-

Table 1. Patient’s Characteristics

<table>
<thead>
<tr>
<th>Pt No.</th>
<th>Age (y) /gender</th>
<th>Diagnosis</th>
<th>NYHA</th>
<th>Vasodilators and inotropic agents</th>
<th>Diuretics</th>
<th>Oxygen inhalation</th>
<th>mean PAP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35/M</td>
<td>Takayasu’s arteritis</td>
<td>II</td>
<td>BPS, CCB, ISDN</td>
<td>+</td>
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<td>54</td>
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<tr>
<td>2</td>
<td>36/F</td>
<td>PPH</td>
<td>III</td>
<td>iv PGI\textsubscript{1}</td>
<td>+</td>
<td></td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>61/F</td>
<td>PTE</td>
<td>IV</td>
<td>iv PGE\textsubscript{2}, iv DOA, iv DOB, CCB</td>
<td>+</td>
<td></td>
<td>43</td>
</tr>
<tr>
<td>4</td>
<td>37/M</td>
<td>PPH</td>
<td>IV</td>
<td>iv PGI\textsubscript{1}, iv DOA, iv PDE III In</td>
<td>+</td>
<td>+</td>
<td>64</td>
</tr>
<tr>
<td>5</td>
<td>47/F</td>
<td>PTE</td>
<td>II</td>
<td>BPS, CCB</td>
<td>+</td>
<td>+</td>
<td>44</td>
</tr>
<tr>
<td>6</td>
<td>36/F</td>
<td>SJS</td>
<td>II</td>
<td></td>
<td>+</td>
<td></td>
<td>26</td>
</tr>
<tr>
<td>7</td>
<td>22/F</td>
<td>PorPH</td>
<td>II</td>
<td></td>
<td>+</td>
<td></td>
<td>44</td>
</tr>
<tr>
<td>8</td>
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<td>PTE</td>
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<td>iv PGI\textsubscript{1}, CCB</td>
<td>+</td>
<td>+</td>
<td>42</td>
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<tr>
<td>9</td>
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<td>III</td>
<td></td>
<td>+</td>
<td>+</td>
<td>60</td>
</tr>
<tr>
<td>10</td>
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<td>iv PGI\textsubscript{1}, CCB</td>
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<td>+</td>
<td>86</td>
</tr>
<tr>
<td>11</td>
<td>31/M</td>
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<td>iv PGI\textsubscript{1}, ACE In</td>
<td>+</td>
<td></td>
<td>31</td>
</tr>
<tr>
<td>12</td>
<td>29/M</td>
<td>PTE</td>
<td>II</td>
<td></td>
<td>+</td>
<td></td>
<td>50</td>
</tr>
<tr>
<td>13</td>
<td>22/F</td>
<td>PPH</td>
<td>III</td>
<td></td>
<td>+</td>
<td></td>
<td>70</td>
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<tr>
<td>14</td>
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<td>II</td>
<td></td>
<td>+</td>
<td></td>
<td>56</td>
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<tr>
<td>15</td>
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<td>PTE</td>
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<td>BPS, CCB</td>
<td>+</td>
<td>+</td>
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<tr>
<td>16</td>
<td>52/F</td>
<td>Dermatomyositis</td>
<td>II</td>
<td></td>
<td>+</td>
<td></td>
<td>53</td>
</tr>
<tr>
<td>17</td>
<td>51/F</td>
<td>PPH</td>
<td>II</td>
<td></td>
<td>+</td>
<td></td>
<td>59</td>
</tr>
</tbody>
</table>


Figure 1. Pulse delivery system. See text for details.  
Figure 2. Continuous delivery system. See text for details.
Statistics

hemodynamic variables were measured, the patients underwent measured by the thermodilution technique. After the baseline measured: pulmonary artery pressure (PAP), right atrial pres-

tipped thermodilution catheter (Swan-Ganz thermodilution catheter, Baxter Healthcare, Irvine CA, USA). A radial or femo-
targeting was performed with a triple lumen balloon-tipped thermocatheter (Swan-Ganz thermodilution catheter, Baxter Healthcare, Irvine CA, USA). A radial or femo-

Study protocol

Oral drugs except for beraprost sodium were withheld on the morning of the catheterization. Beraprost was continued until noon. The intravenous administration of vasodilators and inotropic agents were continued during the study. Right heart catheterization was performed with a triple lumen balloon-

Results

The baseline hemodynamic variables and hemodynamic effects of inhaled NO using the pulse and continuous delivery systems are shown in Table 2. C.O. was increased significantly by each delivery system (from 3.7±0.4 l/min to 4.0±0.4 with pulse and to 4.0±0.3 with continuous delivery, both p<0.05). RAP was decreased slightly but significantly by each delivery system (from 10±1 mmHg to 9±1 with pulse and to 8±1 with continuous delivery, both p<0.01). PVR was also decreased significantly by each delivery system (from 1,218±158 dyne-sec-cm⁻² to 1,077±136 with pulse and to 1,037±120 with continuous, both p<0.01). There were no significant changes in mean SAP, mean PAP, and SVR.

All variables are shown as mean±SEM. PCWP: pulmonary capillary wedge pressure, RAP: right atrial pressure, SAP: systemic artery pressure, PVR: pulmonary vascular resistance, SVR: systemic vascular resistance, C.O.: cardiac output, PVR: pulmonary vascular resistance, SVR: systemic vascular resistance, HR: heart rate. *p<0.01, **p<0.05, compared with baseline.

Inhaled NO using both delivery systems decreased PVR without changing SAP significantly. This was the same effect as in some previous reports that studied inhaled NO for patients with pulmonary hypertension (1, 2). In this study, the concentration of inhaled NO using the pulse delivery system was significantly lower than that using the continuous delivery system (4.3±0.6 ppm and 17.3±2.4, respectively p<0.001). During inhaled NO using the pulse delivery system, the concentrations of NO and NO₂ in the expiratory gas were 0.0 ppm as long as the pulse device was synchronized with the patient’s respiratory cycle. The concentration of NO in the expiratory gas, however, transiently increased to 1.49±0.3 (at the maximum 4.6) ppm, but NO could not be detected within 2 minutes and the concentration of NO₂ remained 0.0 ppm when the patient’s respira-

Discussion

Inhaled NO using both delivery systems decreased PVR without changing SAP significantly. This was the same effect as in some previous reports that studied inhaled NO for patients with pulmonary hypertension (1, 2). In this study, the concentration of inhaled NO using the pulse delivery system was 25% of the concentration of inhaled NO using the continuous delivery system. Nevertheless, the degree of hemody-

Table 2. Baseline Hemodynamic Variables and Hemodynamic Effect of Inhaled NO

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Pulse</th>
<th>Continuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCWP (mmHg)</td>
<td>8±1</td>
<td>8±1</td>
<td>8±1</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>10±1</td>
<td>9±1*</td>
<td>8±1*</td>
</tr>
<tr>
<td>mean PAP (mmHg)</td>
<td>55±4</td>
<td>54±4</td>
<td>53±4</td>
</tr>
<tr>
<td>mean SAP (mmHg)</td>
<td>93±4</td>
<td>92±4</td>
<td>94±4</td>
</tr>
<tr>
<td>C.O. (/min)</td>
<td>3.7±0.4</td>
<td>4.0±0.4**</td>
<td>4.0±0.4**</td>
</tr>
<tr>
<td>PVR (dyne-sec-m⁻²)</td>
<td>1,218±158</td>
<td>1,077±136*</td>
<td>1,037±120*</td>
</tr>
<tr>
<td>SVR (dyne-sec-m⁻²)</td>
<td>2,007±163</td>
<td>1,877±173*</td>
<td>1,882±159</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>85±4</td>
<td>84±3</td>
<td>82±3</td>
</tr>
</tbody>
</table>

All variables are shown as mean±SEM. PCWP: pulmonary capillary wedge pressure, RAP: right atrial pressure, SAP: systemic artery pressure, C.O.: cardiac output, PVR: pulmonary vascular resistance, SVR: systemic vascular resistance, HR: heart rate. *p<0.01, **p<0.05, compared with baseline.
showed that a synchronized inspiratory injection system reduced NO formation in mechanically ventilated patients, but such a system was not intended for ambulatory patients (27–29). Also, Katayama et al reported that they succeeded in minimizing the concentration of inhaled NO using a delivery system that injected NO at the beginning of each breath (30). They used a tightly fitting facemask and did not examine air pollution. Their system was therefore not for ambulatory patients that need long-term inhaled NO therapy. Channick et al reported a pulse delivery system consisting of a nasal cannula, pulse device that is used for home oxygen therapy, and a tank of NO lead to a significant improvement in pulmonary hypertension with primary pulmonary hypertension (31). There was no measurable NO or NO2 in the expiratory gas of their system. This result suggested that an NO delivery system does not necessarily require a scavenging system. Their report also suggested that inhaled NO therapy might be used for ambulatory patients, but they did not compare their pulse delivery system with a continuous delivery system in terms of the degree of hemodynamic changes. Ivy et al reported a comparison of the acute hemodynamic effects of inhaled NO using a pulsed nasal cannula delivery with continuous mask delivery in 8 children with pulmonary hypertension (32). The causes of pulmonary hypertension were congenital heart disease with intra-cardiac shunt in 6 patients, altitude-related pulmonary hypertension in one patient and cardiomypathy in one patient. The present subjects were adult patients none of whom had an intra-cardiac shunt. Our study is the only report that compares the acute hemodynamic effects of a pulse delivery system with a nasal cannula and those of a continuous delivery system with a mask in adult patients with precapillary pulmonary hypertension.

Short-term inhaled NO therapy has been tried in cases with various types of pulmonary hypertension including persistent pulmonary hypertension of the newborn (4–7), residual pulmonary hypertension after cardiac surgery (8–12), adult respiratory distress syndrome (13, 14), Eisenmenger syndrome (15, 16), primary pulmonary hypertension (18), pulmonary thromboembolism (19, 20), and rheumatic disease (21, 22).

These reports demonstrated that inhaled NO is an ideal pulmonary vasodilator for patients with pulmonary hypertension. Long-term inhaled NO therapy is, however, not common for patients with pulmonary hypertension, especially awake and ambulatory patients, because of the following reasons. First, inhaled NO forms toxic NO2, which is a metabolic intermediate of NO. Second, the safety of long-term inhaled NO is unknown. Third, inhaled NO therapy requires a large-scale system consisting of a delivery system, scavenging system and monitoring system for nitrogen oxides. Fourth, it is necessary for patients to be intubated or to wear a tightly fitting facemask to prevent leakage of nitrogen oxides to the environment. Therefore, the clinical use of inhaled NO for awake and ambulatory patients with pulmonary hypertension is usually only for estimating pulmonary vasoreactivity by the acute response (2, 3).

The present pulse delivery system included a nasal cannula to enable ambulatory patients to continue to inhale NO as comfortably as possible for a long-term period. Thus, consideration of environmental pollution was necessary because this system has an open circuit. Using the pulse device, the concentrations of NO and NO2 in the expiratory gas were 0.0 ppm as long as the pulse device was synchronized with the patient’s respiratory cycle. This may mean that almost all of the NO gas delivered to the alveoli at the beginning of each inspiration was diffused to the intravascular space and rapidly inactivated by binding hemoglobin. In daily life, if the patient’s respiratory rate rapidly varies in accordance with physical or mental demand, the pulse device may not be able to control the onset and duration of each pulse properly. In such a case, a decrease of the concentration of inhaled NO and increase of the concentration of NO and NO2 in the expiratory gas may occur. In our study, when the patient’s respiratory rate rapidly varied, the concentration of NO increased to 4.6 ppm at the maximum. The increase of the concentration of NO, however, was transient and the concentration of NO2 remained 0.0 ppm. We can regard these NO and NO2 levels in the expiratory gas as within safe limits according to some safety guidelines (33, 34). Because of the diffusion, the concentrations of NO and NO2 in the environmental air would have been even lower, even if the expiratory gas had not been scavenged. This result suggested that we could use our pulse delivery system without a scavenging system, though our pulse delivery system used an open circuit. Moreover, we demonstrated that the degree of hemodynamic change using the pulse delivery system was similar to that when using the continuous delivery system. Therefore, patients with pulmonary hypertension may use an ambulatory delivery system consisting only of a nasal cannula, a pulse device, a tank of NO, and, if necessary, a tank of O2, for long-term pulmonary vasodilation therapy without concern about environmental pollution.

Whether the hemodynamic effect and the safety of our pulse delivery system would persist in long-term NO therapy is unknown because our study was only for 10 minutes. There have been a few reports of the long-term clinical use of inhaled NO, in which inhaled NO was continued from 8 to 12 months (17, 31, 35). More long-term pulmonary vasodilation therapy is needed for most patients with pulmonary hypertension. For the common use of long-term inhaled NO for the patients with pulmonary hypertension, more investigation to ascertain the persistence of its safety and effect are needed.

Limitations
We studied patients with precapillary pulmonary hypertension only in the resting supine position. For the clinical long-term use of our pulse delivery system without a scavenging system, it is unknown whether the expiratory gas would cause problematic air pollution because it is possible that more asynchronies between the patient’s respiratory rate and the pulse device could occur than in our study. Further examinations will be needed before a conclusion can be reached on the problem of air pollution.

No method of measuring C.O. has been considered a gold standard. We measured C.O. by the thermodilution technique. Patients of this study had, however, tricuspid regurgitation aris-
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In the presence of tricuspid regurgitation, the values of C.O. measured by the thermodilution technique may be overestimated because tricuspid regurgitation influences the thermodilution in the right atrium and ventricle. In this study, because neither PAP nor RAP was elevated after NO inhalation, it seems unlikely that the increase of C.O. after inhalation resulted from the increase of tricuspid regurgitation.

**Conclusion**

The present study demonstrated that our pulse delivery system was able to induce a similar hemodynamic effect with a lower concentration of inhaled NO compared with the continuous delivery system. Concerning possible environmental pollution, our pulse delivery system can be used safely without a scavenging system. Thus, for pulmonary vasodilation therapy of ambulatory patients with pulmonary hypertension, an ambulatory delivery system consisting of a nasal cannula, a pulse device, and a tank of NO may be used. Further investigation, however, is necessary before long-term inhaled NO for patients with pulmonary hypertension can come into common use.

**Appendix: calculation formula**

PVR (dyne-sec-cm⁻⁵) and SVR (dyne-sec-cm⁻⁵) were calculated using the following formula: PVR=80×[mean PAP (mmHg)−PCWP (mmHg)]/C.O. ([l/min] and SVR=80×[mean SAP (mmHg)−RAP (mmHg)]/C.O. ([l/min]) where 80 is the conversion factor.

The concentration of inhaled NO (ppm) using the pulse delivery system was calculated using the following formula: flow rate ([l/min]×1,000/respiratory rate (breath/min)/3×concentration of supplied gas (ppm)/tidal volume (ml/breath).

**References**


29) Katayama Y, Higenbottam TW, Cremona G, et al. Minimizing the inhaled dose of NO with breath-by-breath delivery of spikes of concen-


