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Inhaled Nitric Oxide Therapy After Fontan-Type Operations

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Abstract

Purpose. Inhaled nitric oxide (NO) therapy is a newly developed strategy designed to reduce pulmonary vascular resistance after the Fontan-type operation. We reviewed our experience to evaluate its efficacy and true indications.

Methods. We retrospectively examined 47 children who received inhaled NO therapy after the Fontan-type operation between August 1996 and December 2002. The maximal dose of NO ranged from 5 to 30 ppm (median 10 ppm), and the duration of inhaled NO therapy ranged from 5 h to 52 days (median 2 days).

Results. Inhaled NO significantly decreased the central venous pressure (CVP), from 16.2 ± 2.2 to 14.6 ± 2.2 mmHg ($P < 0.0001$), and the transpulmonary pressure gradient between the CVP and left atrial pressure, from 9.9 ± 2.9 to 8.4 ± 2.7 mmHg ($P < 0.0001$). It also increased the systolic systemic arterial pressure from 71.9 ± 15.2 to 76.8 ± 14.5 mmHg ($P < 0.05$). In 26 patients with additional fenestration, inhaled NO led to a significant improvement in SaO_2 from 90.1% ± 9.6% to 93.3% ± 7.9% ($P < 0.01$). However, patients with a CVP <15 mmHg or a transpulmonary pressure gradient <8 mmHg, or both, after the Fontan-type operation, showed no significant changes in hemodynamics during inhaled NO therapy.

Conclusions. We propose that a CVP ≥15 mmHg or a transpulmonary pressure gradient ≥8 mmHg, or both, after Fontan-type operations are appropriate indications for inhaled NO therapy.

Key words Congenital heart disease · Nitric oxide · Fontan-type operation

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Introduction

Inhaled nitric oxide (NO) has been found to produce a significant reduction in both pulmonary arterial pressure and pulmonary vascular resistance, without inducing systemic hemodynamic effects.[1,2] Nitric oxide stimulates guanylate cyclase in pulmonary vascular smooth muscle to produce guanosine 3′,5′-cyclic monophosphate, which induces vascular smooth muscle relaxation.[3] Nitric oxide is deactivated rapidly by combining with hemoglobin and reactive oxygen species, which results in the localized effects of NO.[4] Therefore, inhaled NO has become a new method of treatment to reduce pulmonary vascular resistance after cardiac operations.[5–10]

In recent years, the indications for Fontan-type operations have been extended to include complex cardiac anomalies and high-risk Fontan candidates.[11,12] After the Fontan-type operation, increased pulmonary vascular resistance may severely impair pulmonary perfusion, resulting in low cardiac output, especially in high-risk patients. Studies have shown that NO can remarkably improve the results of Fontan-type operations; however, only a few series of inhaled NO therapy after Fontan type operations have been reported.[13–16] Thus, we reviewed our experience of using this treatment to determine the efficacy of, and appropriate indications, for inhaled NO therapy after Fontan-type operations.

Patients and Methods

Patients

Between August 1996 and December 2002, 75 patients underwent Fontan-type operations in our hospital, 47 of whom received inhaled NO therapy postoperatively, and were the subjects of this study. The patients ranged in age from 1 to 16 years (median 4 years) and weighed

Table 1. Preoperative risk factors for the Fontan-type operation

Risk factors	NO (+) (n = 47)	NO (−) (n = 28)	
Age <2 years old at the time of surgery	7	3	NS
Heterotaxy syndrome	14	6	NS
Atrioventricular valve regurgitation	4	1	NS
Deformity of the pulmonary artery	15	8	NS
PA index (Nakata) <200	8	3	NS
Mean pulmonary artery pressure >20 mmHg	5	3	NS
Pulmonary artery resistance >3 Wood units	2	6	NS
Ejection fraction of the systemic ventricle <60%	19	8	NS
Arrhythmia	1	1	NS
Anomalous pulmonary venous return	8	1	NS
Anomalous systemic venous return	6	3	NS

NO, nitric oxide; NS, not significant; PA, pulmonary artery

from 5.4 to 60.3 kg (median 14 kg). The primary malformation was a univentricular heart in 14 patients, tricuspid atresia in 12, double outlet right ventricle in 10, mitral atresia or severe mitral stenosis with a hypoplastic left ventricle in 7, pulmonary atresia with intact ventricular septum in 2, and multiple ventricular septal defects in 2. Preoperatively, the mean pulmonary artery resistance was 1.9 ± 0.7 Wood units (range 0.5–3.8 Wood units) and the mean pulmonary artery pressure was 13.9 ± 3.2 mmHg (range 8–20 mmHg). We performed total cavopulmonary anastomosis with an intra-atrial conduit in 9 patients, and an extracardiac Fontan operation in 38 patients. A fenestration was created between the conduit and the atrium in 26 patients. The cardiopulmonary bypass time ranged from 0 to 356 min (median 153 min). The preoperative risk factors for a Fontan-type operation in the patients who received inhaled NO therapy and those who did not are shown in Table 1. There were no significant differences in the preoperative risk factors between these two groups.

Inhaled NO Therapy

The indications for NO inhalation were based on the clinical judgment of the attending surgeons and anesthetists, and included low blood pressure, high central venous pressure, a high transpulmonary pressure gradient, and low urine output. All patients were intubated and managed conventionally with sedation, inotropic agents such as dopamine, dobutamine, or epinephrine, and intravenous vasodilators such as nitroglycerine, prostaglandin E1, chlorpromazine, or amrinone. Respiration was adjusted to establish an arterial carbon dioxide tension of about 40 mmHg and an arterial pH of about 7.40.

Nitric oxide was administered from stock cylinders containing 997 ppm NO balanced with nitrogen gas, and delivered into the inspiratory limb of the ventilatory circuit close to the endotracheal tube, using an airway sampling adapter. Expired gases were scavenged using wall suctioning. The maximal dose of inhaled NO ranged from 5 to 30 ppm (median: 10 ppm). Methemoglobin levels were determined before, and every 6–8 h during NO treatment. We monitored central venous pressure (CVP), left atrial pressure (LAP), systemic arterial pressure, systemic arterial oxygen saturation (SaO_2) by pulse oximetry, and electrocardiograms continuously in all patients.

Nitric oxide therapy was started in the operation room in 33 patients and in the intensive care unit in the other 14 patients. The duration of NO therapy ranged from 5 h to 52 days (median 2 days).

Statistical Analysis

Normally distributed data are expressed as the mean ± standard deviation, and data not normally distributed are expressed as medians, with interquartile ranges. The effects of NO on hemodynamic parameters and oxygenation were compared with baseline findings by the paired t-test. A P value of less than 0.05 was considered significant.

Results

Mortality

There were six deaths resulting from low cardiac output syndrome in three patients, thrombosis in two, and tracheal bleeding in one. One patient with asplenia syndrome and severe dysfunction of the systemic ventricle with an ejection fraction of 47.6%, and another with severely unbalanced pulmonary arteries died of low cardiac output syndrome. One patient who had undergone five prior palliative procedures died of thrombosis in the

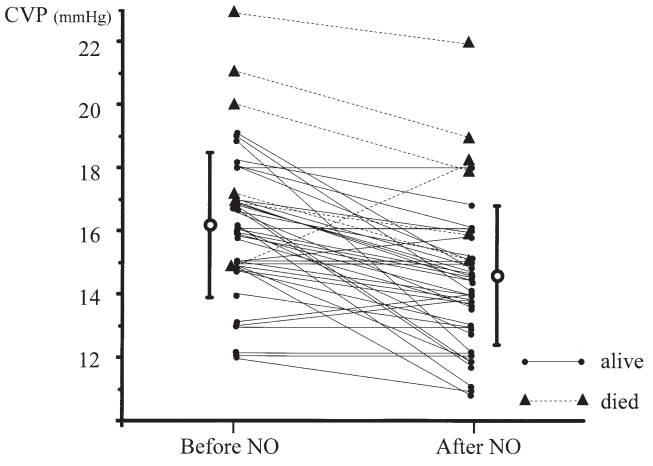


Fig. 1. Central venous pressure before and after initiation of inhaled nitric oxide therapy. *CVP*, central venous pressure; *NO*, nitric oxide

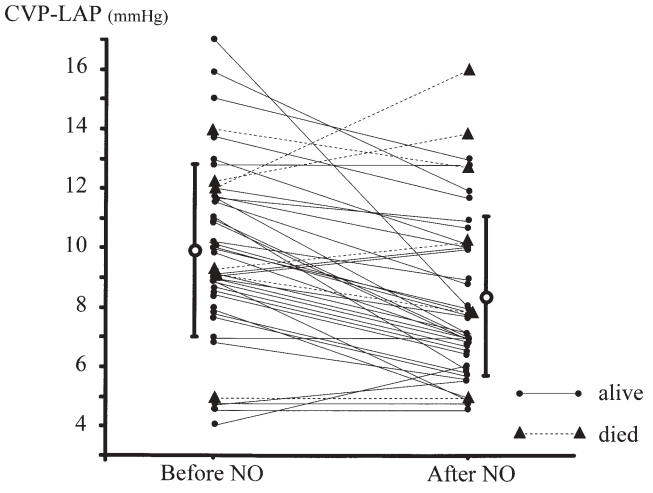


Fig. 2. Transpulmonary pressure gradient before and after initiation of inhaled nitric oxide therapy. *LAP*, left atrial pressure

central pulmonary artery, which had been reconstructed with an expanded polytetrafluoroethylene graft. Retrospectively, these three patients should not have been considered as suitable candidates for a Fontan-type operation.

Toxicity of NO Inhalation

There was no clinical evidence of toxicity during the administration of inhaled NO in any patient. The methemoglobin level was always less than 1.5% in all of the patients.

Effects of Inhaled NO Therapy

In the collective 47 patients, inhaled NO significantly decreased the CVP from 16.2 ± 2.2 to 14.6 ± 2.2 mmHg ($P < 0.0001$) (Fig. 1), and the transpulmonary pressure gradient between CVP and LAP from 9.9 ± 2.9 to 8.4 ± 2.7 mmHg ($P < 0.0001$) (Fig. 2). The systolic systemic arterial pressure increased from 71.9 ± 15.2 to 76.8 ± 14.5 mmHg ($P < 0.05$). The LAP remained unchanged before and after the initiation of NO inhalation. In 26 patients with additional fenestration, inhaled NO led to a significant improvement in SaO_2 from 90.1 ± 9.6 to 93.3 ± 7.9% ($P < 0.01$).

As shown in Figs. 1 and 2, inhaled NO had no effect on the CVP or transpulmonary pressure gradient in some patients. In patients with a CVP <15 mmHg or a transpulmonary pressure gradient <8 mmHg after the Fontan-type operation, there were no significant changes in the hemodynamic parameters during NO inhalation. Moreover, in four of the six patients who died, the transpulmonary pressure gradient did not decrease after the initiation of inhaled NO therapy, and in five of these six patients there were no changes in SaO_2 during NO inhalation.

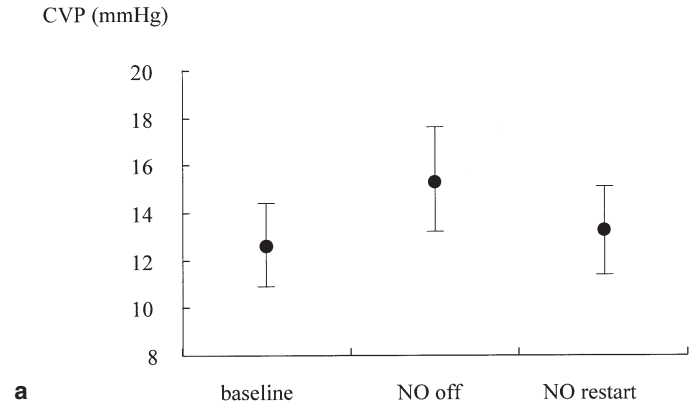
Rebound Phenomenon

In 17 patients, the CVP and transpulmonary pressure gradient increased immediately after discontinuation of the inhaled NO therapy ($P < 0.0001$); however, the hemodynamic parameters recovered quickly after its reinstitution (Fig. 3). All of these 17 patients were successfully weaned from NO inhalation after their hemodynamic state became stable.

Discussion

Elevated pulmonary vascular resistance is a widely recognized risk factor for the outcome of Fontan-type operations.[12] Adequate pulmonary perfusion and cardiac output are critically dependent on low pulmonary vascular resistance and normal systemic ventricular function. However, in the early postoperative period, pulmonary vascular resistance is unstable because of the deleterious effects of cardiopulmonary bypass on pulmonary endothelial function.[15,16] Even minor elevations in pulmonary vascular resistance may result in critical low cardiac output syndrome, especially in high-risk patients.

Inhaled NO acts only locally in the pulmonary smooth muscle cells, producing selective pulmonary vasodilation.[1,2,4] Although inhaled NO may result in an improvement in pulmonary perfusion by selective pulmonary vasodilation, the clinical use of inhaled NO after Fontan-type operations has not been studied carefully in a large series of patients. Yahagi et al.,[13] Zobel



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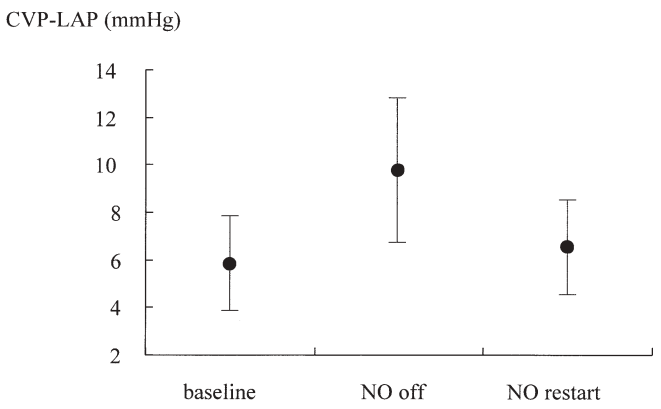

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Fig. 3a,b. Rebound phenomenon. **a** Changes in central venous pressure resulting from the discontinuation and reinstitution of inhaled nitric oxide therapy. **b** Changes in transpulmonary pressure gradient resulting from the discontinuation and reinstitution of inhaled nitric oxide therapy

et al.,[14] Goldman et al.,[15] and Gamillscheg et al.[16] reported series of 18, 11, 10, and 9 patients, respectively. They all found that inhaled NO therapy decreased the CVP and transpulmonary pressure gradient between CVP and LAP. We confirmed that NO inhalation significantly decreased the CVP and transpulmonary pressure gradient and significantly increased systolic systemic arterial pressure in our patients after Fontan-type operations. Moreover, the methemoglobin levels measured several times each day did not reach clinically relevant values. These results encouraged us to give patients NO inhalation after Fontan-type operations.

We also observed that inhaled NO improved oxygenation in patients after the fenestrated Fontan operation. An interatrial fenestration may prevent systemic venous congestion and low cardiac output by shunting blood flow from the right to the left side of the heart.[12,17] However, if the shunting blood flow becomes excessive because of elevated pulmonary vascular resistance, it may result in severe hypoxemia and a vicious cycle caused by hypoxemia-induced pulmonary vasoconstriction.[15] A decrease in pulmonary vascular resistance after NO inhalation might increase the pulmonary blood flow and improve oxygenation. Our findings are in accordance with those of Goldman et al.,[15] who reported that inhaled NO led to improved oxygenation in patients after the fenestrated Fontan operation.

On the other hand, some of our patients showed no response to inhaled NO. Fullerton et al.[18] reported that the response to inhaled NO varies among patients who have pulmonary hypertension with or without valvular heart disease. They suggested that the intracellular mechanisms by which NO inhalation induces pulmonary vasodilation are impaired in patients with valvular heart disease.[18] Snow et al.[4] found that NO inhalation did not induce any hemodynamic effect in patients with normal pulmonary pressure and resistance after coronary bypass surgery. They suggested that because pulmonary endothelial function was not impaired and basal endogenous NO production was maintained in these patients, exogenous NO had little further effect.[4] Goldman et al.[15] noted that inhaled NO led to a significant improvement in oxygenation and the transpulmonary pressure gradient in desaturated patients after the fenestrated Fontan operation, and that patients with lower baseline SaO_2 had greater responses to inhaled NO. They concluded that patients with an SaO_2 <85% or a transpulmonary pressure gradient >12 mmHg, or both, after the fenestrated Fontan-type operation should be given a trial of inhaled NO.[15] In our series, there were no significant changes in the hemodynamic parameters during NO inhalation in patients with a CVP <15 mmHg or a transpulmonary pressure gradient <8 mmHg, and we are now convinced that these patients did not need NO. On the other hand, NO inhalation did not result in any improvement in the six patients who died, because if the cause of their circulatory or respiratory disturbance could not be treated, their mortality was not influenced by inhaled NO therapy.

In 17 of the 47 patients in this series, the CVP and transpulmonary pressure gradient increased immediately after NO inhalation was discontinued, and we had to restart it. Several authors have described the rebound phenomenon after the withdrawal of NO inhalation.[19,20] Nitric oxide inhalation may cause an inhibitory feedback over endogenous NO synthesis, and if exogenous NO is abruptly withdrawn, because its life span is so short, the NO concentration in the pulmonary circulation will decrease abruptly without time to recover endogenous synthesis, which may result in pulmonary vasoconstriction. Cueto et al.[20] proposed a gradual withdrawal of NO inhalation with careful monitoring of oxy-

genation and hemodynamic parameters, even if NO has not been clearly effective. Thus, we now gradually decrease the concentration of inhaled NO, and temporarily increase the percentage of oxygen in inspired gas to maintain the same oxygenation before and after the discontinuation of NO inhalation.

In conclusion, the findings of this study clearly showed that NO inhalation improved hemodynamics and oxygenation in children after Fontan-type operations. We propose that the appropriate indications for NO inhalation after Fontan-type operations are a CVP $\geq$15 mmHg or a transpulmonary pressure gradient $\geq$8 mmHg, or both.

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