Artificial Organs
21(1):17–20, Blackwell Science, Inc., Boston

Effects of Inhaled Nitric Oxide on Postoperative Pulmonary Circulation in Patients with Congenital Heart Disease

Junki Matsui, Naoki Yahagi, Keiji Kumon, Hideaki Hayashi, Yasuhiko Watanabe, Masaki Haruna, Hironobu Tanigami, *Toshikatsu Yagihara, *Shinichi Takamoto, and †Tetsuro Kamiya

*Surgical Intensive Care Unit, Departments of *Cardiovascular Surgery, and Department of †Pediatrics, National Cardiovascular Center, Osaka, Japan*

Abstract: We studied 22 patients with residual pulmonary hypertension or symptoms of postoperative pulmonary hypertensive crisis. They received low-dose inhalation (10 ppm) of nitric oxide (NO), a selective pulmonary vasodilator, after total correction for congenital heart anomalies. Fifteen minutes of NO inhalation improved the pulmonary circulation and lessened the imbalance in the ventilation-perfusion ratio in both groups. Thus, NO inhalation is effective in the treatment of pulmonary hypertension and in the prevention of pulmonary hypertensive crises after total correction for congenital heart anomalies. All patients continued to receive NO therapeutically. The duration of such therapeutic NO inhalation was well correlated with postoperative Qp/Qs ($p = 0.014$) and Rp/Rs ($p = 0.029$). **Key Words:** Nitric oxide—Congenital heart disease—Cardiac surgery—Pulmonary hypertension—Pulmonary hypertensive crises.

The resistance of the pulmonary circulation is a very important factor in the management of patients who have undergone total repair of congenital heart anomalies. Inhalation of nitric oxide (NO), a selective pulmonary vasodilator (1), is a newly developed strategy for the treatment of primary pulmonary hypertension of the newborn (PPHN) (2), primary pulmonary hypertension (PPH) of the adult (3,4), pulmonary hypertension (PH) in congenital cardiac disease (5), cardiac surgical patients (6–9), and patients with Fontan circulation (10), and right ventricular failure in patients with a pulmonary transplantation (11), or a left ventricular assist system (12).

In this study, we evaluated the hemodynamic changes that followed inhalation of a low concentration (10 parts per million [ppm]) of NO in patients with residual PH and with the symptoms of pulmonary hypertensive crisis (PHC) after total correction for congenital heart anomalies. After the study period, all patients received additional inhalation of NO therapeutically. We also assessed the factors influencing the required duration of therapeutic NO inhalation.

Received March 1996.
Address correspondence and reprint requests to Dr. Naoki Yahagi, Surgical Intensive Care Unit, National Cardiovascular Center, Suita, Osaka 565, Japan.

MATERIALS AND METHODS

The survey involved a total of 22 patients between the ages of 7 days and 10 months who had PH or symptoms of PHC after total correction for their congenital heart anomalies (Table 1). Of the 22 patients, 17 showed pulmonary hypertension of $Pp/Ps > 0.4$ during the operation after total correction (PH group). The remaining 5 patients did not show residual PH but showed symptoms of hypoxia, hypotension, bradycardia, and increased right atrial pressure (RAP) associated with a stress event, such as tracheal suction, after surgical corrections (PHC group).

Values for the Pao_2/Fio_2 ratio (P/F ratio), RAP, left atrial pressure (LAP), and mean arterial pressure (mAP) just before NO inhalation were designated pre-NO. Values at the end of 15 min after NO inhalation were designated post-NO.

Inhaled NO (400 ppm in nitrogen; Taiyo-Toyo Sanso Co. Ltd., Osaka, Japan) was introduced via a T-piece connector downstream of a humidifier in the inspiratory limb of a breathing system connected to a constant flow respirator (BP2001, Bear Medical Systems, Inc., Riverside, California, U.S.A., or Newport E150, Newport Medical Instruments, Inc., Newport Beach, California, U.S.A.). It was initially administered at a concentration of 10 ppm for 15 min (10). All patients were supported

TABLE 1. *Patient characteristics*

Patient no.	Sex	Age	Diagnosis[a]	Precorrection			Postcorrection			Status[b]	Duration of inhaling NO (h)
				Pp/Ps	Qp/Qs	Rp/Rs	Pp/Ps	Qp/Qs	Rp/Rs		
PH group											
1	M	12 days	TGA(I)	0.71			0.42	1.25	0.33	A	58
2	F	18 days	CoA, DORV, PDA, PFO				0.47	1.00	0.47	A	389
3	F	16 days	TAPVC(Ia + III)	0.89	1.18	0.75	0.64	1.00	0.64	A	111
4	F	17 days	TAPVC(III)				0.51	1.00	0.51	A	47
5	M	17 days	TAPVC				1.06	1.50	0.66	D	208
6	M	2 months	CoA, DORV, AS	0.86	2.50	0.34	0.44	1.30	0.34	D	147
7	F	3 months	CoA, VSD, SAS, PFO	1.08	3.10	0.24	0.62	1.50	0.41	A	203
8	F	4 months	VSD, ASD, PDA	0.83	3.74	0.22	0.54	0.98	0.55	A	57
9	F	7 months	DORV, CoA, PDA	0.46	2.26	0.18	0.40	1.56	0.24	A	444
10	M	8 months	VSD	0.83	2.65	0.26	0.41	0.83	0.50	A	10
11	F	10 months	CAVC	0.92	2.08	0.34	0.40	1.38	0.28	A	86
12	F	8 days	LV tumor	0.50			0.80	1.00	0.80	A	259
13	M	8 months	VSD, PFO	0.90	2.44	0.30	0.40	1.20	0.31	A	48
14	M	7 days	TGA(I), PDA				0.80	1.02	0.78	A	401
15	M	26 days	CoA, VSD, PDA	0.59	13.59	0.03	0.40	1.04	0.35	A	90
16	F	14 days	IAA, VSD, PDA, SAS				0.87	1.86	0.47	D	342
17	F	20 days	CoA, VSD, PFO	0.78	9.16	0.09	0.41	0.98	0.41	A	29
Mean ± SD											170 ± 140
PHC group											
1	F	1 months	TGA(II), PDA	0.71	2.99	0.24				A	241
2	M	10 months	cTGA, VSD	0.82	4.45	0.15	0.39	1.24	0.32	A	97
3	F	5 months	DORV	1.00	3.70	0.22	0.39	1.20	0.33	A	55
4	F	2 months	DORV, ASD	0.92	4.24	0.22	0.27	1.15	0.24	A	52
5	M	18 days	VSD, PDA, PFO	0.82			0.39	1.26	0.32	A	82
Mean ± SD											105 ± 70

[a] TGA, transposition of great arteries; CoA, coarctation of aorta; DORV, double outlet of right ventricle; PDA, patent ductus arteriosus; PFO, patent foreman ovale; TAPVC, total anomalous of pulmonary venous connection; AS, aortic stenosis; VSD, ventricle septal defect; SAS, subaortic stenosis; ASD, atrial septal defect; CAVC, common atrioventricular canal; LV, left ventricle; cTGA, corrected transposition of great arteries.
[b] A, alive; D, dead.

with dobutamine or dopamine (3–5 μg/kg/min). The inspired oxygen fraction was adjusted to keep Pa_{O_2} at approximately 100 mm Hg.

All patients continued to receive the gas therapeutically. The dose was gradually decreased to 1 ppm, and the gas was discontinued when clinical recovery allowed. The duration of inhalation was from 29 to 444 h, with an average of 169 h, in the PH group and from 52 to 241 h, with an average of 140 h, in the PHC group. The effect on the duration of NO inhalation of each hemodynamic parameter, including preoperative catheterization values and the intraoperative measurements taken after surgical correction, was analyzed statistically. The intraoperative hemodynamic measurements were made after patients were weaned from cardiopulmonary bypass. Qp/Qs and Rp/Rs were calculated using the standard formulae:

$$Qp/Qs = (CaO_2 - C_{RA}O_2)/(C_{LA}O_2 - C_{PA}O_2)$$
$$Rp/Rs = (Pp/Ps)/(Qp/Qs)$$

Blood oxygen content was measured using a cooxymeter (OSM3; Radiometer, Copenhagen, Denmark).

In addition, the blood methemoglobin level was measured several times a day during NO inhalation. The concentrations of NO and NO_2 were measured just before the intratracheal tube was inserted several times a day. The concentration of NO_2 did not exceed 0.1 ppm at any time.

All values are presented as mean ± standard deviation (SD). A paired Student's *t*-test was used for statistical analysis of the values before and after the 15 min inhalation of NO. Simple linear regression analysis was used to compare the duration of therapeutic NO inhalation with measurements obtained by preoperative catheterization and with measurements of intraoperative hemodynamic parameters; p values of less than 0.05 were considered significant.

RESULTS

Compared with the PHC group, which had no PH, the PH group exhibited low RAP, LAP, and mAP and poor oxygenation before NO administration (Figs. 1 and 2). In the PH group, the post-NO value for RAP was significantly lower than the pre-NO value. LAP and mAP increased slightly after NO inhalation, but not significantly. The post-NO value for the P/F ratio was significantly higher than the pre-NO value (Fig. 1).

Qualitatively similar, but more pronounced changes were obtained in the PHC group. In addition, no recurrence of severe PHC was found in any patient after NO administration (Fig. 2).

All patients continued to receive NO therapeutically. Table 2 shows that the duration of NO inhalation was well correlated with postoperative Qp/Qs ($p = 0.014$)

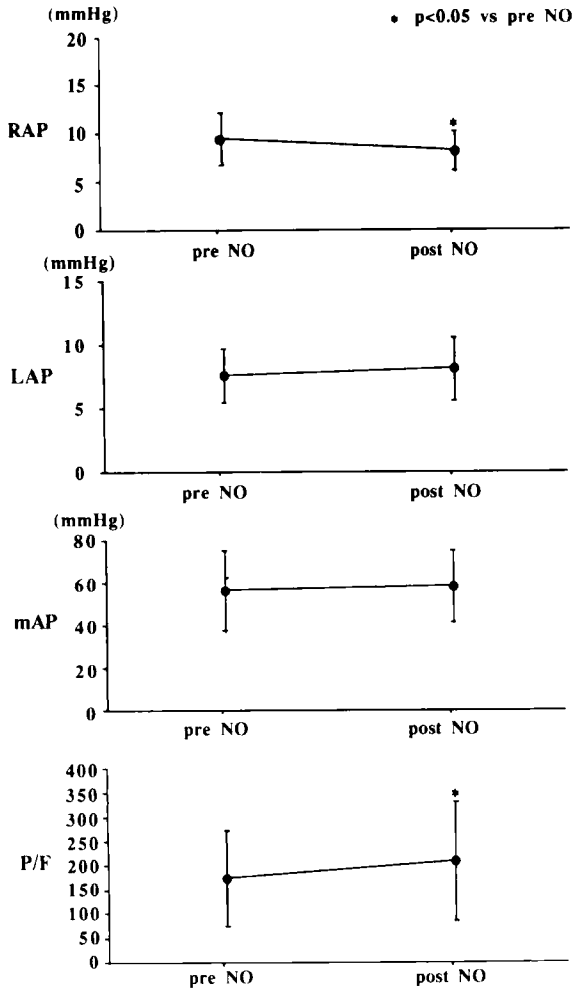

FIG. 1. Changes in RAP, LAP, mAP, and P/F ratio between pre- and post-NO inhalation in the pH group are shown.

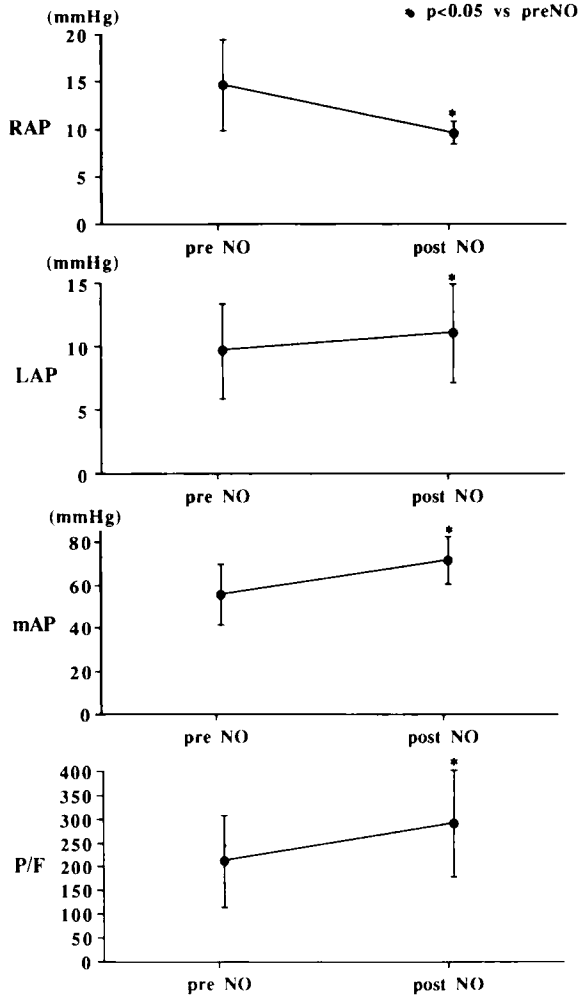

FIG. 2. Changes in RAP, LAP, mAP, and P/F ratio between pre- and post-NO inhalation in the PHC group are shown.

and Rp/Rs ($p = 0.029$). The blood methemoglobin level was 2.5 ± 1.5% in the pH group and 3.4 ± 2.2% in the PHC group. In some patients, the maximum level reached was above 5%.

DISCUSSION

Our study demonstrates that inhaling 10 ppm NO for a 15 min period significantly reduced RAP without decreasing mAP in the PH group and significantly reduced the RAP while increasing mAP and LAP in the PHC group, both groups being pediatric patients who underwent surgical correction for congenital heart disease (Figs. 1 and 2). Congenital cardiac disease that increases pulmonary blood flow or causes pulmonary venous obstruction may induce hypertrophy of pulmonary artery smooth muscle and pulmonary vasoconstriction (5). Of the 17 patients in the PH group, 10 were neonates, and of the 5 patients in the PHC group, 2 were neonates. The remaining 10 patients in both groups had the greatest level of PH. Despite the heterogeneity of the patient population, inhaling NO produced a consistent improvement in the pulmonary circulation.

All patients continued to receive NO therapeutically. Table 2 shows that the duration of this NO inhalation was well correlated with the postoperative Qp/Qs ($p = 0.014$) and Rp/Rs ($p = 0.029$) in the PH group. The presence of a residual left-to-right shunt through the periphery of a closure patch for atrial or ventricular septal

TABLE 2. *Factors' effects on duration of inhaling NO in PH group*

	p
Precorrection	
Pp/Ps	0.236
Qp/Qs	0.167
Rp/Rs	0.421
Postcorrection	
Pp/Ps	0.606
Qp/Qs	0.014
Rp/Rs	0.029

defect and persistent pulmonary hypertension were indications for prolonging NO inhalation. A residual intracardiac shunt may be the deteriorative factor for the circulation, because it increases the preload for both ventricles and may cause heart failure. There was no good correlation between preoperative parameters, including Pp/Ps, Qp/Qs, or Rp/Rs, and the duration of NO inhalation. In this PH group, 3 patients who had either mild Qp/Qs (1.3 and 1.56 in Patients 6 and 9, respectively) or high Rp/Rs (0.66 in Patient 5) showed symptoms of a PHC, despite extended inhalation of NO. We advise caution in the use of inhaled NO for a patient who has a high Rp/Rs and also some residual intracardiac shunt because there may be no advantage in using the pulmonary dilator.

Existing therapies for PHC are manual hyperventilation with oxygen, adequate sedation, use of a vasodilator (13,14), and extracorporeal membrane oxygenation (15). In our study, NO inhalation was initiated early against the symptoms of PHC, and all cases showed improvement in their hemodynamic values within the short study period. Furthermore, prolonged inhalation of a low dose of less than 10 ppm NO prevented the recurrence of PHC in the patients who had a Pp/Ps of less than 0.4 although 3 patients in the PH group exhibited recurrent PHCs during extensive NO inhalation.

The rise in the P/F ratio occurred probably because NO dilated pulmonary vessels and improved capillary flow over well-ventilated alveoli, improved the imbalance in the ventilation-perfusion ratio, and improved the blood gas status (16,17). In the PH group, the present results were obtained by improving the prolonged PH. More pronounced changes were obtained in the PHC group who showed symptoms of pulmonary constriction.

It is unlikely that there was any pulmonary injury, which would be associated with NO_2 inhalation, in the patients who were treated with less than 10 ppm NO for 10–444 h. In adults, it is very rare for NO administration to cause an increase in the blood methemoglobin level above 2%, but many of our infants showed a higher level. Therefore, the blood methemoglobin levels in infants should be frequently measured during NO inhalation.

CONCLUSION

Low-dose inhalation of 10 ppm NO improved the pulmonary circulation and lessened the imbalance in the V/P ratio of pediatric patients with residual PH or symptoms of a postoperative PHC after surgical repair. NO inhalation is effective in the treatment of PH and in the prevention of PHC after total correction for congenital heart anomalies. All patients continued to receive NO therapeutically. The duration of such therapeutic NO inhalation was well correlated with postoperative Qp/Qs and Rp/Rs.

Acknowledgment. This study was supported by Special Coordination Funds for Promoting Science and Technology (Encouragement System of COE) from the Science and Technology Agency of Japan.

REFERENCES

1. Frostell C, Fratacci M-D, Wain JC. Inhaled nitric oxide: A selective pulmonary vasodilator reversing hypoxic pulmonary vasoconstriction. *Circulation* 1991;83:2038.
2. Kinsella JP, Neish SR, Shaffer E, Abman SH. Low dose inhalational nitric oxide in persistent pulmonary hypertension of the newborn. *Lancet* 1992;340:819–20.
3. Roberts JD Jr, Polander DM, Lang P, Zapol WM. Inhaled nitric oxide in persistent pulmonary hypertension of the newborn. *Lancet* 1992;340:818–9.
4. Pepke Zaba J, Higenbottam TW, Tuan Dinh-Xuan A, Stone D, Wallwork J. Inhaled nitric oxide as a cause of selective pulmonary vasodilation in pulmonary hypertension. *Lancet* 1991;338:1173–4.
5. Roberts JD Jr, Lang P, Bigatello LM, Vlahakes GJ, Zapol WM. Inhaled nitric oxide in congenital heart disease. *Circulation* 1993; 87:447–53.
6. Rich GF, Murphy GD, Roos CM, Johns RA. Inhaled nitric oxide: Selective pulmonary vasodilation in cardiac surgical patients. *Anesthesiology* 1993;78:1028–35.
7. Miller OI, James J, Elliott MJ. Intraoperative use of inhaled low-dose nitric oxide. *J Thorac Cardiovasc Surg* 1993;105:550–1.
8. Allman KG, Young JD, Stevens JE, Archer LN. Nitric oxide treatment for fulminant pulmonary hypertension. *Arch Dis Child* 1993; 69:449–50.
9. Girard C, Lehot J-J, Pannetier J-C. Inhaled nitric oxide after mitral valve replacement in patients with chronic pulmonary artery hypertension. *Anesthesiology* 1992;77:880.
10. Yahagi N, Kumon K, Tanigami H, Watanabe Y, Ishizaka T, Yamamoto F, Nishigaki K, Matsuki O, Yagihara T. Inhaled nitric oxide for the postoperative management of Fontan-type operation. *Ann Thorac Surg* 1994;57:1371–3.
11. Adatia I, Lillelei C, Arnold JH, Thompson JE, Palazzo R, Fackler JC, Wessel DL. Inhaled nitric oxide in the treatment of postoperative graft dysfunction after lung transplantation. *Ann Thorac Surg* 1994;57:1311–8.
12. Yahagi N, Kumon K, Nakatani T, Matsui J, Sasako Y, Isobe F, Sakakibara Y, Kitoh Y, Nagata S, Haruna M, Watanabe Y, Takamoto S. Inhaled nitric oxide for the management of acute right ventricular failure in patients with a left ventricular assist system. *Artif Organs* 1995;19:557–8.
13. Hopkins RA, Bull C, Haworth SG, de-Leval MR, Stark J. Pulmonary hypertensive crises following surgery for congenital heart defects in young children. *Eur J Cardiothorac Surg* 1991;5: 628–34.
14. Scott JP, Higenbottam TW, Smyth RL, Wallwork J. Acute pulmonary hypertensive crisis in a patient with primary pulmonary hypertension treated by both epoprostenol (prostacyclin) and nitroprusside. *Chest* 1991;99:1284–5.
15. Klein MD, Shaheen KW, Whittlesey GC, Pinsky WW, Arciniegas E. Extracorporeal membrane oxygenation for the circulatory support of children after repair of congenital heart disease. *J Thorac Cardiovasc Surg* 1990;100:498–505.
16. Frostell CG, Blomqvist H, Hedenstierna G. Inhaled nitric oxide selectively reverses human hypoxic pulmonary vasoconstriction without causing systemic vasodilation. *Anesthesiology* 1993;78: 427–35.
17. Rossaint R, Falke KS, Lopez F, Slama K, Pison U, Zapol WM. Inhaled nitric oxide for the adult respiratory distress syndrome. *N Engl J Med* 1993;328:399–405.