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Inhalation of Low-Dose Nitric Oxide to Evaluate Pulmonary Vascular Reactivity in Children with Congenital Heart Disease

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Abstract. The objective of this study was to investigate the efficacy of low-dose nitric oxide (NO). The study used fifteen consecutive Japanese preoperative patients (7 males and 8 females) with congenital heart disease and pulmonary hyptertension (mean pulmonary arterial pressure >30 mmHg), 6 of these patients had Down's syndrome. Hemodynamic measurements were taken in room air, 100% oxygen, 5 and 40 parts per million NO (NO5 and NO40) by inhalation. The differences between two observations within the same group were determined by the two-tailed paired *t*-test. A pulmonary vascular resistance (R_p) regression curve was constructed by using linear regression analysis. The percentage change in pulmonary arterial pressure per systemic arterial pressure (P_p/P_s) with NO40 (P_p/P_s-40) exceeded that of P_p/P_s-5 ($p < 0.0001$). The percentage change for the R_p with NO40 (Rp-40) was larger than that for the R_p-5 ($p = 0.0003$). The percentage change of P_p/P_s-5 and that with oxygen were similar ($p = 0.266$). The relationship between R_p-5 and R_p-40 was linear. In conclusion, the effects of NO5 were equivalent to 100% oxygen but less than NO40. NO5 should initially be used to test pulmonary reactivity. If there is no response, patients should still be given NO40.

Key words: Nitric oxide — Congenital heart disease — Pulmonary hypertension — Oxygen — Pulmonary vascular resistance

The inhalation of nitric oxide (NO), a selective pulmonary vasodilator, is used to evaluate and treat patients with pulmonary hypertension (PH) secondary to congenital heart disease (CHD) [1, 6, 11, 12]. In general, minimally effective doses of inhaled NO are recommended to prevent lung injury [14]. Data of cardiac catheterizations with inhaled NO have been reported [1, 6, 11, 12]. However, the effect of low-dose NO [<40 parts per million (ppm)] had not been studied.

To investigate the efficacy of low-dose NO we compared the efficacy of 5 ppm NO to that of 40 ppm NO, which was previously used in cardiac catheterization, and pure oxygen, the agent conventionally used to treat PH.

Patients

Fifteen consecutive Japanese patients (7 males and 8 females) with CHD and pulmonary hypertension were studied. Their mean age was 18 ± 23 months. PH was diagnosed when the mean pulmonary artery pressure exceeded 30 mmHg [8]. These patients had the following heart diseases: ventricular septal defect (VSD, $n = 7$), VSD and persistent ductus arteriosus (PDA, $n = 2$), VSD and atrial septal defect (ASD) ($n = 1$), VSD and pulmonary stenosis ($n = 1$), ASD ($n = 1$), double-outlet right ventricle and PDA ($n = 1$), single ventricle and PDA ($n = 1$), and PDA ($n = 2$). Six of the patients also had Down's syndrome. Written informed consent was obtained from the parents and/or guardians of each child before catheterization. The ethics committee of our hospital approved this study.

All the patients underwent surgery to correct the CHD. Complete surgical correction was achieved in 14 patients and pulmonary artery banding was done in 1 patient (case 3). Three (cases 1, 5, and 7) of the 14 patients who had complete surgical corrections developed PH postoperatively and were treated with inhaled NO. In case 1, NO was administered for 8 days at a maximal inhaled NO concentration of 12.5 ppm. Case 5 received inhaled NO to a maximal level of 20 ppm, along with other conventional therapies, namely, hyperventilation with 100% oxygen, deep sedation, and catecholamine administration. Unfortunately, this patient died on the fifth postoperative day. The PH crisis in case 7 resolved with the inhalation of NO at a maximal level of 11.8 ppm for 9 days. Overall, the surgical outcome was satisfactory in all patients except one who underwent surgery.

Methods

The Fick method was used to calculate the flow and resistance for the systemic and pulmonary circulations. The patients were premedicated with tricofos sodium (100 mg/kg, oral), pethidine hydrochloride [1

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mg/kg, intravenous (i.v.)], hydroxyzine hydrochloride (0.75 mg/kg, i.v.), and pentazocine (0.4 mg/kg, i.v.) if the sedation was not enough.

The system for administrating NO by inhalation reported by Winberg et al. [12] was used in this study. We placed a transparent plexiglas hood over the head of the infant and sealed it around the neck with a thin plastic wrap. Room air was continuously drawn through the system by a vacuum pump. The hood effluent was collected and the oxygen concentration determined.

At first right heart catheterization and left atrial pressure measurements were performed with inhalation of room air. When the left artrial pressure was not obtained, the pulmonary wedge pressure was recorded instead. The systemic blood pressure was monitored through the femoral artery. Then pure oxygen was delivered into the hood, and simultaneous recordings of systemic and pulmonary pressure were obtained during the inhalation of oxygen. Next, NO was delivered when the cardiopulmonary parameters and arterial blood gas levels had returned to baseline after the delivery of oxygen had been stopped. NO from a stock concentration of 400 ppm, kept in a cylinder of pure nitrogen (Taiyo Toyo Sanso Corporation, Japan), was added to the system at a flow rate calculated to deliver inspired NO at fractions of 5 ppm or of 40 ppm.

Manometry and oxymetry data of all the patients were obtained for room air, 100% oxygen, and each concentration of NO during stable conditions. Blood samples for determination of saturated level of oxygen and methemoglobin were analyzed with an OSM II analyzer (Radiometer, Denmark). The concentrations of NO and nitrogen dioxide (NO_2), collected in a hood placed over the patient's head, were monitored with the Pac II analyzer (Dräger, Germany). Oxygen consumption was estimated and was assumed to be constant throughout the study [9]. We calculated pulmonary arterial pressure per systemic arterial pressure (P_p/P_s) in the presence of room air (P_p/P_s-B), pure oxygen (P_p/P_s-O), 5 ppm NO (P_p/P_s-5), and 40 ppm NO (P_p/P_s-40) for each individual. Pulmonary vascular resistance (R_p) levels were also calculated in indexed Wood units · m^2 in room air (R_p-B), 5 ppm NO (R_p-5), and 40 ppm NO (R_p-40). The effects of 5 ppm NO, 40 ppm NO, and oxygen on the percentage change in the P_p/P_s and R_p levels from baseline were subsequently compared with each other. Patients with Down's syndrome were compared with those without Down's syndrome to determine whether this syndrome affected PH.

Statistical Analysis

The data are expressed as mean ± SD. Differences between two observations within the same group were determined by performing the two-tailed paired *t*-test. An R_p regression curve was constructed by using linear regression analysis with the StatView 4.0 software package. Differences between the groups with and without Down's syndrome were determined by the two-tailed unpaired *t*-test. The level of variance between the groups was examined by using an *F* test. A level of $p < 0.05$ was accepted as statistically significant.

Results

Baseline measurements and changes in P_p/P_s and R_p are shown in Table 1. During the inhalation of room air the ratio of pulmonary flow per systemic flow (Q_p/Q_s) was 2.1 ± 0.90, whereas the P_p/P_s-B was 0.76 ± 0.15 and the R_p-B was 4.5 ± 2.7 Wood units · m^2. The percentage change in P_p/P_s-40 (−22 ± 11%) significantly exceeded that of P_p/P_s-5 (−13 ± 8.8%) ($p < 0.0001$; Fig. 1). In addition, the percentage change for the R_p-40 measurement (−41 ± 14%) was significantly larger than that for the R_p-5 (26 ± 11%) ($p = 0.0003$; Fig. 2). The P_p/P_s and R_p levels observed with both concentrations of NO were reduced in all cases, with the drop in all indices at 40 ppm NO being larger than that with 5 ppm.

An assessment of pulmonary vasoreactivity with 5 ppm NO inhalation and 100% oxygen showed similar effects on pulmonary circulation. Figure 3 shows that the percentage change of P_p/P_s-5 was not different from that obtained with P_p/P_s-O (−13.2 ± 8.8% vs −14.8 ± 8.1%, $p = 0.266$). The effect of inhaled NO was compared between patients with and without Down's syndrome (Table 2). There were no statistically significant differences in age, P_p/P_s-B, R_p-B, or the percentage change in P_p/P_s-O, P_p/P_s-5, P_p/P_s-40, R_p-5, or R_p-40 between the two groups. The maximal arterial partial pressure of carbon dioxide yielding no hypoventilation during catheterization and also did not significantly differ between the groups. The inhaled oxygen concentration was reduced to 1.6% of its maximum level when NO was inhaled. The maximum methemoglobin level was 1.3%, and that of NO_2 was below the level of detection.

Discussion

Measurements of P_p/P_s and R_p are used as markers of PH in patients with CHD [2, 5]. When a patient is suspected of having severe PH, the pulmonary vasodilator capacity is assessed by the observed drop in both P_p/P_s and R_p upon the administration of oxygen, of a vasodilator such as trazoline hydrochloride, or of a calcium channel blocker [2]. However, with the administration of 100% oxygen by inhalation, reliable R_p measurements cannot be calculated because the Fick principle is not applicable when the systemic venous oxygen saturation is increased by oxygen inhalation [7]. Any changes in the P_p/P_s ratio in the presence of oxygen administration may not be correlated with the R_p level since oxygen dilates the pulmonary vascular bed and increases the Q_p/Q_s ratio. From a viewpoint of side effects, a common complication of the intravenous administration of a vasodilator [3] is a concomitant fall in systemic vascular resistance and arterial hypotension. Vasodilators also nonselectively dilate the vessels proximal to underventilated alveoli in the lung, aggravating the ventilation–perfusion mismatch and contributing to the arterial hypoxemia. Thus, one cannot satisfactorily assess PH when oxygen or intravenous vasodilators are being administered.

In contrast, by calculating R_p only with oxymetry when NO was administered by inhalation one could easily monitor the pulmonary vasodilatory function because systemic venous oxygen saturation was not increased in this study. Systemic hypotension, arterial hypoxemia, and other complications were not detected. Therefore, the inhalation of NO is useful in evaluating PH, because it is a selective pulmonary vasodilator.

Table 1. Patient characteristics, with responses to room air, oxygen, and NO inhalations

Case no.	Diagnosis		Age (months)	P_p/P_s				R_p (Wood $\overline{U} \cdot m^2$)			Operation	PH crisis[a]/ NO inhalation[b]	Outcome
				Baseline	Oxygen	5 ppm NO	40 ppm NO	Baseline	5 ppm NO	40 ppm NO			
1	VSD, PDA	Down	7	1.0	0.91	0.99	0.98	8.2	5.9	5.8	TC	+/+	S
2	VSD	Down	10	0.59	0.44	0.39	0.35	2.2	1.2	0.92	TC		S
3	SV, PDA	Down	3	0.68	0.65	0.65	0.59	2.3	2.0	1.9	PAB		S
4	PDA	Down	7	0.76	0.68	0.64	0.57	4.7	3.9	2.3	TC		S
5	DORV, PDA	Down	8	0.95	0.84	0.87	0.80	10.6	9.6	6.6	TC	+/+	D
6	ASD	Down	83	0.63	0.50	0.50	0.41	4.6	3.3	2.0	TC		S
7	VSD		8	1.0	0.86	0.93	0.86	8.9	7.9	5.3	TC	+/+	S
8	VSD		9	0.81	0.69	0.70	0.59	2.9	2.0	1.5	TC		S
9	VSD		10	0.83	0.57	0.68	0.56	4.5	3.1	2.5	TC		S
10	VSD		12	0.68	0.63	0.64	0.63	3.0	2.2	1.3	TC		S
11	VSD		29	0.49	0.44	0.44	0.38	1.4	1.2	1.2	TC		S
12	VSD, ASD		59	0.63	0.50	0.54	0.49	4.1	3.1	2.3	TC		S
13	VSD, PDA		4	0.82	0.79	0.77	0.74	3.6	2.8	2.8	TC		S
14	VSD, PS		11	0.76	0.57	0.56	0.53	4.3	2.7	2.3	TC		S
15	PDA		4	0.76	0.66	0.67	0.56	1.8	1.0	1.0	TC		S
	Mean ± SD		18 ± 23	0.76 ± 0.15	0.65 ± 0.15	0.66 ± 0.17	0.60 ± 0.18	4.5 ± 2.7	3.5 ± 2.5	2.7 ± 1.8			

Down, Down's syndrome; VSD, ventricular septal defect; PDA, persistent ductus arteriosus; SV, single ventricle; DORV, double-outlet right ventricle; ASD, atrial septal defect; TC, total correction; PAB, pulmonary artery banding; S, survived; D, deceased; SD, standard deviation.

[a] Severe clinical deterioration by acute rise in pulmonary arterial pressure after surgical repair.

[b] A therapy with inhaled NO to treat a pulmonary hypertension after surgical repair.

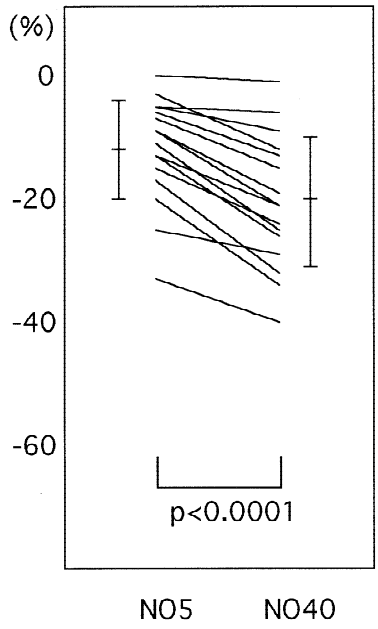

Fig. 1. Percentage change in P_p/P_s.

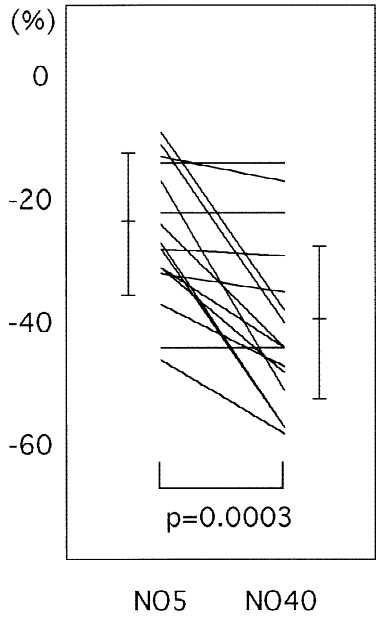

Fig. 2. Percentage change in R_p.

Our results demonstrate that significantly greater reductions in levels of P_p/P_s ($p < 0.0001$) and R_p ($p = 0.0048$) were evident at 40 ppm NO than at 5 ppm NO. The linear relationship was revealed between R_p-5 and R_p-40 (Fig. 4). Since we did not use a randomized dosing protocol, one cannot be certain that the greater response to NO40 was definitely due to the higher dose or whether it was an effect of time, having started at NO5. To avoid

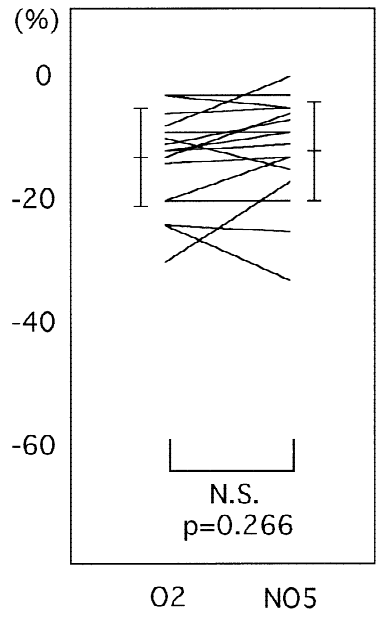

Fig. 3. Percentage change in P_p/P_s.

Table 2. Data and results in patients with and without Down's syndrome

	Patients with Down's syndrome	Patients without Down's syndrome	*p* value
Age (months)	20 ± 31	16 ± 18	0.79
P_p/P_s-B	0.77 ± 0.17	0.75 ± 0.14	0.86
R_p-B (Wood $\overline{U} \cdot m^2$)	5.4 ± 3.3	3.8 ± 2.2	0.28
Change in P_p/P_s-0 (%)	14 ± 7.8	16 ± 8.7	0.66
Change in P_p/P_s-5 (%)	14 ± 12	13 ± 6.6	0.77
Change in P_p/P_s-40 (%)	22 ± 14	21 ± 9.0	0.92
Change in R_p-5 (%)	24 ± 13	27 ± 11	0.59
Change in R_p-40 (%)	42 ± 16	40 ± 13	0.84
Maximum PCO_2	44 ± 6.5	43 ± 3.2	0.66

Data are expressed as mean ± standard deviation.

lung injury, administration of a lower concentration of NO is recommended [14]. Inhaling NO at higher levels causes marked methemoglobinemia and pulmonary edema and has caused death in humans. Therefore, patients should be initially tested with 5 ppm NO. If they show a good response then it is unnecessary to expose them to the higher dose of 40 ppm NO. However, there were cases (cases 4, 5, and 7) that demonstrated only a mild decrease (<20%) in R_p-5, but a much larger response (>35%) in R_p-40. Those patients failing to respond to the lower dose of 5 ppm should still be given a trial of 40 ppm NO to determine the full potential of reversibility of their pulmonary hypertension. It may even be that higher doses are still needed to fully test reactivity, although this has not been tested in this study.

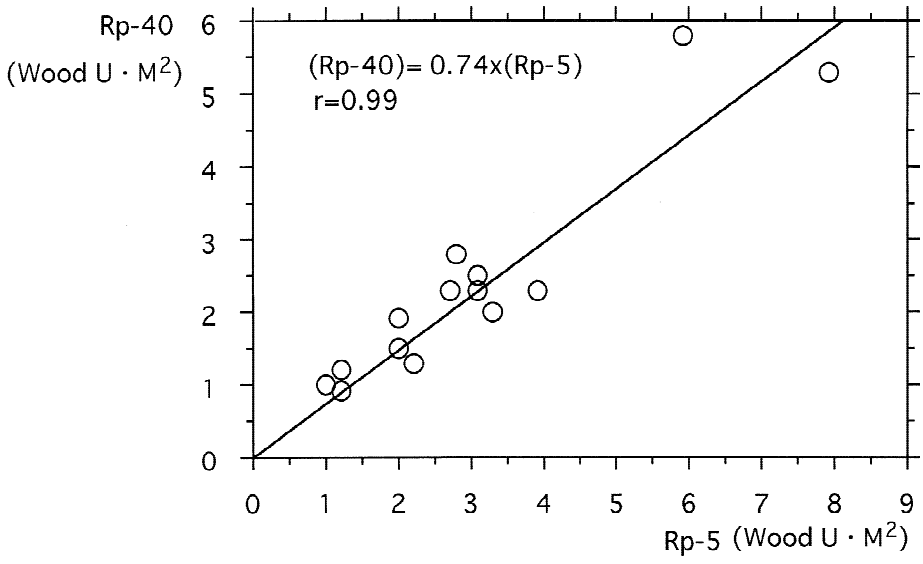

Fig. 4. Linear relationship between R_p-5 and R_p-40.

One patient (case 5) died of postoperative PH crisis. This individual had the smallest percentage decrease in R_p-5 (9%) but exhibited good pulmonary vasodilatation with inhalation of 40 ppm NO—a drop in the R_p-40 of 38% from baseline. An additional study investigating the surgical indications is required for the patients with severe PH who respond poorly to 5 ppm NO inhalation but respond well to 40 ppm NO inhalation.

The causes of pulmonary hypertension in patients with Down's syndrome and CHD are multiple, including the obstructive sleep apnea syndrome [10], pulmonary vascular disease [13], and pulmonary hypoplasia [4]. The responses to NO inhalation in the six patients with Down's syndrome were comparable to those of the nine patients without this syndrome. The pulmonary vasoreactivity to NO inhalation did not differ between the two groups.

In conclusion, the P_p/P_s obtained with 5 ppm NO inhalation and 100% oxygen showed similar effects in the patients with CHD and PH. The change in the R_p level with 5 ppm NO inhalation is less than that with 40 ppm NO: there was a linear correlation between the R_p levels with inhalation of 5 ppm NO and that of 40 ppm NO. Therefore, the inhalation of 5 ppm NO, which is safer than that of 40 ppm NO, should be initially performed for assessing pulmonary vascular reactivity in preoperative patients with CHD. However, patients failing to respond to the lower dose of 5 ppm NO should still be given a trial of 40 ppm NO to determine the full potential of reversibility of their pulmonary hypertension.

References

1. Berner M, Beghetti M, Spahr-Schopfer I, Oberhansli I, Friedli B (1996) Inhaled nitric oxide to test the vasodilator capacity of pulmonary vascular bed in children with long-standing pulmonary hypertension and congenital heart disease. *Am J Cardiol 77*:532–535
2. Bush A, Busst CM, Haworth SG, et al. (1988) Correlations of lung morphology, pulmonary vascular resistance, and outcome in children with congenital heart disease. *Br Heart J 59*:480–485
3. Bush A, Busst CM, Knight WB, Shinebourne EA (1988) Comparison of the hemodynamic effects of epoprostenol (prostacyclin) and tolazoline. *Br Heart J 60*:141–148
4. Cooney TP, Thurlbeck WM (1982) Pulmonary hypoplasia in Down's syndrome. *N Engl J Med 19*:1170–1173
5. Davis NJ, Shinebourne EA, Scallan MJ, Sopwith TA, Denison DM (1984) Pulmonary vascular resistance in children with congenital heart disease. *Thorax 39*:895–900
6. Day RW, Lynch JM, Shaddy RE, Orsmond GS (1995) Pulmonary vasodilatory effects of 12 and 60 parts per million inhaled nitric oxide in children with ventricular septal defect. *Am J Cardiol 75*:196–198
7. Feustel PJ, Perkins RJ, Oppenlander JE, Stratton HH, Cohen IL (1994) Feasibility of continuous oxygen delivery and cardiac output measurement by application of the Fick principle. *Am J Respir Crit Care Med 149*:751–758
8. Fullerton DA, Jaggers J, Wollmering MM, et al. (1997) Variable response to inhaled nitric oxide after cardiac surgery. *Ann Thorac Surg 63*:1251–1256
9. La Farge CG, Miettinen OS (1970) The estimation of oxygen consumption. *Cardiovasc Res 4*:23–30
10. Marcus CL, Keens TG, Bautista DB, von Pechmann WS, Ward SLD (1991) Obstructive sleep apnea in children with Down syndrome. *Pediatrics 88*:132–139
11. Roberts JD Jr, Lang P, Bigatello LM, Vlahakes GJ, Zapol WM (1993) Inhaled nitric oxide in congenital heart disease. *Circulation 87*:447–453
12. Winberg P, Lundell BPW, Gustafsson LE (1994) Effect of inhaled nitric oxide on raised pulmonary vascular resistance in children with congenital heart disease. *Br Heart J 71*:282–286
13. Yamaki S, Horiuchi T, Sekino Y (1983) Quantitative analysis of pulmonary vascular disease in simple cardiac anomalies with Down syndrome. *Am J Cardiol 51*:1502–1506
14. Zapol WM, Rimar S, Gillis N, Marletta M, Bosken CH (1994) Nitric oxide and the lung. *Am J Respir Crit Care Med 149*:1375–1380