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Usefulness of Nitric Oxide Treatment for Pulmonary Hypertensive Infants during Cardiac Anesthesia

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Background: **The beneficial effect of inhaled nitric oxide (NO) on pulmonary hypertension is well known. However, the indications for NO inhalation therapy for pulmonary hypertension associated with congenital heart lesions are still unclear. The aim of the current study was to seek a measure that would predict the effectiveness of inhaled NO in infants undergoing cardiac surgery.**

Methods: **Forty-six infants with pulmonary hypertension were studied. Pulmonary vascular resistance (PVR) measured at the time of cardiac catheterization was used as an indicator and compared with pulmonary arterial pressure/systemic blood pressure ratio (Pp/Ps) at the time of weaning from cardiopulmonary bypass. The effect of 40 ppm of inhaled NO for 15 min was evaluated in patients whose Pp exceeded systemic values.**

Results: **Preoperative PVR correlated positively with Pp/Ps at the time of weaning from cardiopulmonary bypass ($r^2 = 0.86$; $P < 0.05$; $n = 46$). A Pp/Ps greater than or equal to 1 was not observed in any cases in which the preoperative PVR values were less than 7 Wood units m^2; Pp/Ps ratio greater than or equal to 1 occurred in four patients. Each of these had PVR values greater than 7 Wood units m^2. Three of these patients who had PVR values in the 7–12 Wood units m^2 range were responsive to inhaled NO. The fourth patient, whose PVR value was greater than 15 Wood units m^2, was unresponsive. Lung biopsy specimens were obtained in two patients whose preoperative PVR values were greater than 10 Wood units m^2.**

Conclusion: **Preoperative PVR correlates reasonably well with postbypass Pp/Ps.**

NITRIC Oxide (NO) is a well-known pulmonary vasodilator[1] and has been reported to be effective in the treatment of neonatal pulmonary hypertension[2,3] and postoperative pulmonary hypertension in patients with congenital heart defects.[4,5] However, the indications for NO inhalation are not yet well established for infants with pulmonary hypertension during general anesthesia for cardiac surgery. Oxygen inhalation,[6] hyperventilation,[7] pulmonary vasodilators,[8–11] and high-dose fentanyl[12,13] have been shown to be effective in preventing postoperative pulmonary hypertension, which may develop during weaning from cardiopulmonary bypass (CPB). In contrast, the efficacy of NO inhalation in addition to these treatments has not been established.

Pulmonary vascular resistance (PVR) is widely regarded as a measure of the severity of pulmonary vascular degeneration and pulmonary hypertension, and several reports have referred to its possible relevance to the development and prognosis of postoperative pulmonary hypertension.[14–19] The purpose of the current study was to investigate whether postbypass pulmonary hypertension would correlate with preoperative PVR and to evaluate whether NO inhalation would be effective treatment for postbypass pulmonary hypertension in these patients.

Materials and Methods

The study was approved by an institutional review committee (Iwate Medical University Memorial Heart Center, Iwate, Japan), and informed consent was obtained for each patient. Fifty infants with congenital heart disease who underwent cardiac catheterization at Iwate Medical University Memorial Heart Center or Nagano Prefectural Children's Hospital from April 1995 to April 2000, were enrolled. The mean pulmonary arterial pressure was 25 mmHg or more.

Anesthesia for Cardiac Catheterization

Cardiac catheterization was scheduled within 2 weeks before surgery. Chloral hydrate (50 mg/kg administered orally), pethidine hydrochloride (1 mg/kg administered subcutaneously), and hydroxyzine hydrochloride (1 mg/kg administered subcutaneously) were given as premedication. Anesthesia was induced by intravenous injection of atropine sulfate (0.02 mg/kg), pentazocine (0.5 mg/kg), and lidocaine (1.0 mg/kg), followed by inhalation of sevoflurane and tracheal intubation. It was then maintained with inhalation of approximately 0.5% sevoflurane at an oxygen concentration of 21% during spontaneous respiration. After anesthesia was stabilized, cardiac catheters were introduced with additional local anesthesia. Peripheral arterial hemoglobin oxygen saturation was monitored continuously with a pulse oximeter (Durapalse PA2100; NEC, Tokyo, Japan), and end-tidal carbon dioxide and sevoflurane concentrations were monitored with capnography (PM8050; Drager, Lubeck, Germany). If the end-tidal carbon dioxide concentration exceeded 50 mmHg, ventilation was assisted according to the result of blood gas analysis. Blood pressure, hemoglobin concentration, and oxygen saturation were measured, followed by calculation of PVR, pulmonary arterial pressure/systemic blood pressure ra-

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tio (Pp/Ps), and pulmonary blood flow/systemic blood flow ratio ($\dot{Q}p/\dot{Q}s$) by the Fick formula:

$$\dot{Q}s = \text{Oxygen consumption}/Cao_2 - Cvo_2\ (/m^2)$$

$$\dot{Q}p = \text{Oxygen consumption}/Cpvo_2 - Cpao_2\ (/m^2)$$

$$PVR = mPAP - mPCWP/\dot{Q}p \quad (1)$$

where $\dot{Q}s$ is systemic blood flow (cardiac index; liters per minute per square meter), Cao_2 is systemic arterial oxygen content (milliliters per liter), $C\bar{v}o_2$ is mixed venous oxygen content (milliliters per liter), $\dot{Q}p$ is pulmonary blood flow, $Cpvo_2$ is pulmonary venous oxygen content, $Cpao_2$ is pulmonary arterial oxygen content, PVR is pulmonary vascular resistance (Wood units m^2), mPAP is mean pulmonary arterial pressure (millimeters of mercury), and mPCWP is mean pulmonary capillary wedge pressure (millimeters of mercury). Oxygen consumption was estimated from nomograms based on surface area or age and heart rate.[20] Oxygen content was calculated by multiplying the hemoglobin oxygen-carrying capacity (13.6 ml O_2/l) and hemoglobin oxygen saturation.

Histopathologic Evaluation of Lung Biopsy

When PVR was greater than or equal to 10 Wood units m^2, lung biopsy was performed during general anesthesia to determine whether surgical treatment was necessary.

In addition to the Heath-Edwards classification,[21] an index of pulmonary vascular disease (IPVD), as proposed by Yamaki *et al.*,[14] was evaluated. IPVD was defined by the formula:

$$\text{Index} = (1 \times n1) + (2 \times n2) + (3 \times n3) + (4 \times n4) /n1 + n2 + n3 + n4 \quad (2)$$

where n_1, n_2, n_3, and n_4 are the numbers of pulmonary arterial sections bearing the respective scores. A score from 1 to 4 was given to each arterial section according to the following histologic findings: (1) no intimal reaction, (2) cellular intimal proliferation, (3) fibroelastic proliferation of intima, and (4) partial and total destruction of media. This index varied in theory from 1.0 to 4.0.

Anesthesia for Cardiac Surgery

The same premedication as described above were given. Anesthesia was induced by intravenous injection of atropine sulfate (0.02 mg/kg), fentanyl citrate (5 μg/kg), lidocaine (1.0 mg/kg), and vecuronium bromide (0.3 mg/kg) followed by tracheal intubation, and was maintained with intravenous injection of fentanyl citrate at a total dose of 100 μg/kg, midazolam at a total dose of 0.2 mg/kg, and vecuronium bromide as needed.

During CPB, mean arterial pressure was maintained at approximately 30 mmHg by manipulation of pump flow between 100 and 180 ml/kg, bolus administration of chlorpromazine hydrochloride (total dose of 1 mg/kg), and continuous infusion with nitroglycerine (3–6 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and alprostadil (prostaglandin E1; 0.05–0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$). During weaning from CPB, pulmonary arterial pressure (Pp), ascending aortic pressure (Ps), and left atrial pressure were directly monitored. Weaning was attempted by continuous infusion with dopamine hydrochloride (5–15 $\mu g \cdot kg^{-1} \cdot min^{-1}$), dobutamine hydrochloride (5–15 $\mu g \cdot kg^{-1} \cdot min^{-1}$), milrinone (0.2–0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$), along with continuous use of vasodilators, 100% oxygen inhalation, and hyperventilation. Drugs were administered to keep left atrial pressure less than 12 mmHg and systolic ascending aortic pressure greater than 60 mmHg. If pulmonary arterial pressure exceeded ascending aortic pressure ($Pp/Ps > 1$) in the presence of maximal doses of vasodilators, 40 ppm NO was added to the inspired gas mixture. NO was supplied from NO cylinders at 500 ppm through a flow meter (Taiyotoyo Co., Ltd., Osaka, Japan). Exhaled gas was collected by a TMS-100 (Taiyotoyo Co., Ltd.) placed distally to the endotracheal tube to monitor NO and NO_2 concentrations.

The Pp/Ps ratios at the time of weaning from CPB were compared with preoperative PVR values, Pp/Ps ratios, and $\dot{Q}p/\dot{Q}s$ ratios measured during cardiac catheterization to find any possible correlation between these parameters. In the four patients who developed postbypass pulmonary hypertension that exceeded systemic pressure, Pp/Ps ratios were calculated before and 15 min after inhalation of 40 ppm NO. During NO inhalation, breathing conditions and the use of pulmonary vasodilators were kept constant.

Statistical Analysis

Data are presented as mean ± SD. The regression curve of PVR was depicted by Stat View 4.0 software (Abacus Concepts, Berkeley, CA). Significant differences between groups were tested by the Scheffé F test, and $P < 0.05$ was considered a significant difference.

Results

Data were obtained from 46 patients (25 male, 21 female). The mean age was 5.1 ± 2.8 months (range, 1–15 months) at the time of surgery, and mean weight was 5.0 ± 1.8 kg (range, 2.7–11.5 kg). The mean PVR measured during cardiac catheterization was 4.1 ± 2.7 Wood unit m^2 (range, 0.7–15 Wood unit m^2). Mean Pp/Ps ratio was 0.7 ± 0.2 (range, 0.25–1), and mean $\dot{Q}p/\dot{Q}s$ ratio was 2.8 ± 1.2 (range, 1–5.3). The mean Pp/Ps ratio at the time of weaning from CPB was 0.5 ± 0.2 (range, 0.25–1.2). Data are presented in table 1. Preoperative PVR correlated well with Pp/Ps at the time of weaning from CPB ($r^2 = 0.86$; $P < 0.05$; n = 46;

Table 1. Data for All Patients

Case (No.)	Age (month)	PVR (Wood unit m^2)	$\dot{Q}p/\dot{Q}s$	Pp/Ps	post-Pp/Ps	Diagnosis
1	1	2.1	5.0	0.55	0.30	VSD ASD PDA
2	3	1.5	4.1	0.83	0.25	VSD PDA CoA
3	2	2.9	3.2	1.00	0.32	VSD ASD
4	5	0.7	1.8	0.70	0.20	VSD
5	7	6.0	2.6	0.50	0.50	cECD
6	4	3.0	2.5	0.99	0.50	VSD ASD
7*	6	15.0	1.0	0.88	1.20	cECD
8	2	1.5	4.1	0.98	0.30	VSD PDA CoA
9	4	2.3	2.8	0.45	0.40	VSD
10	2	2.1	3.2	0.94	0.25	VSD
11*	4	7.6	3.0	1.00	1.00	VSD ASD
12	2	1.4	4.1	0.87	0.20	VSD
13	4	3.6	2.4	0.77	0.40	VSD ASD
14	6	5.3	1.6	1.00	0.60	VSD ASD
15	6	5.5	5.3	0.90	0.60	VSD ASD PDA
16	13	5.0	2.4	0.87	0.50	DORV
17	6	1.1	1.9	0.55	0.20	VSD
18	11	3.3	3.5	0.67	0.50	DORV
19	5	5.9	1.2	0.75	0.60	VSD PDA
20	3	2.1	2.1	0.47	0.30	VSD
21	4	5.1	2.2	1.00	0.60	VSD
22	3	2.0	5.3	0.76	0.25	VSD ASD PDA
23	6	6.8	5.0	0.60	0.60	cECD
24	5	2.6	1.4	0.53	0.30	VSD PS
25*	8	12.0	1.2	1.00	1.20	cECD
26	2	1.5	4.5	0.79	0.25	VSD APW
27	10	5.5	1.1	0.80	0.60	VSD ASD
28	3	2.2	3.1	0.77	0.25	VSD
29	4	3.0	1.7	0.49	0.60	VSD
30	4	4.5	2.5	0.66	0.60	VSD ASD
31*	5	7.4	4.0	0.70	1.00	cECD
32	6	2.8	2.0	0.44	0.35	VSD
33	4	2.6	2.3	0.42	0.30	VSD
34	3	3.1	4.5	0.75	0.35	VSD ASD
35	7	3.9	1.7	0.83	0.40	VSD PS
36	5	4.3	2.9	0.85	0.50	iECD
37	3	5.1	2.0	0.48	0.55	VSD
38	15	2.3	3.0	0.41	0.25	iECD
39	8	6.5	1.9	0.69	0.50	VSD
40	6	2.1	1.1	0.38	0.25	VSD PS
41	7	3.1	2.2	0.45	0.40	VSD
42	4	5.3	3.0	0.43	0.55	VSD ASD PDA
43	4	3.2	2.2	0.38	0.35	VSD
44	5	5.1	2.5	1.00	0.50	VSD
45	3	3.8	2.6	0.66	0.35	VSD PDA
46	5	2.6	2.1	0.61	0.32	VSD

* Patients who developed post-Pp/Ps ≧ 1.

PVR = pulmonary vascular resistance; $\dot{Q}p/\dot{Q}s$ = pulmonary blood flow/systemic blood flow; Pp/Ps = pulmonary arterial pressure/systemic blood pressure; post-Pp/Ps = Pp/Ps at the time of weaning from cardiopulmonary bypass; VSD = ventricular septal defect; ASD = atrial septal defect; PS = pulmonary arterial stenosis; PDA = patent ductus arteriosus; CoA = coarctation of the aorta; APW = aortopulmonary window; DORV = double outlet right ventricle; iECD = incomplete endocardial cushion defects; cECD = complete endocardial cushion defects.

fig. 1), but preoperative Pp/Ps did not correlate with Pp/Ps at the time of weaning from CPB (fig. 2). Preoperative $\dot{Q}p/\dot{Q}s$ did not correlate with Pp/Ps at the time of weaning from CPB (fig. 3).

Characteristics of patients who developed postbypass pulmonary hypertension that exceeded systemic pressure are presented in table 2. In no case was Pp/Ps greater than or equal to 1 seen in a patient with preoperative PVR values less than 7 Wood units m^2. In three patients (cases no. 11, 25, 31), Pp/Ps ratios decreased significantly after NO inhalation (1.07 ± 0.12 *vs.* 0.67 ± 0.06; $P < 0.05$; n = 3). Case no. 7, who showed a PVR value of 15 Wood units m^2, did not respond to inhaled NO. He failed to wean from CPB and died. After obtaining informed consent, lung autopsy was performed in this patient.

The histopathologic evaluation of pulmonary arterial walls in two cases whose preoperative PVR values were 10 Wood units m^2 or more were as follows: case no. 7: type of intimal reaction was fibrous, state of media of

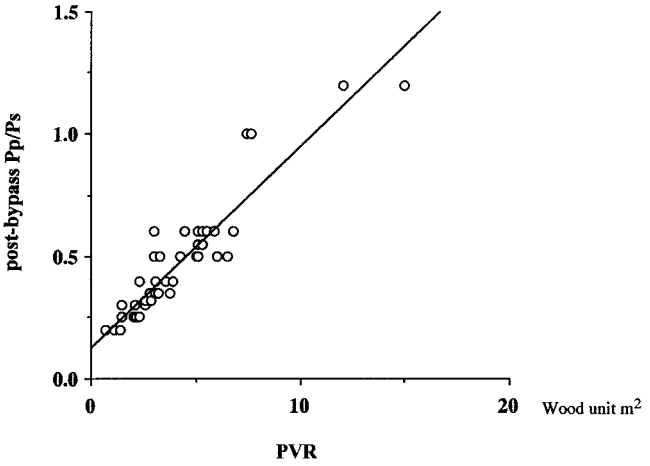

Fig. 1. Relation between preoperative pulmonary vascular resistance (PVR) and pulmonary arterial pressure/systemic blood pressure ratio (Pp/Ps) at the time of weaning from cardiopulmonary bypass (r^2 = 0.86; P = 0.0001; n = 46).

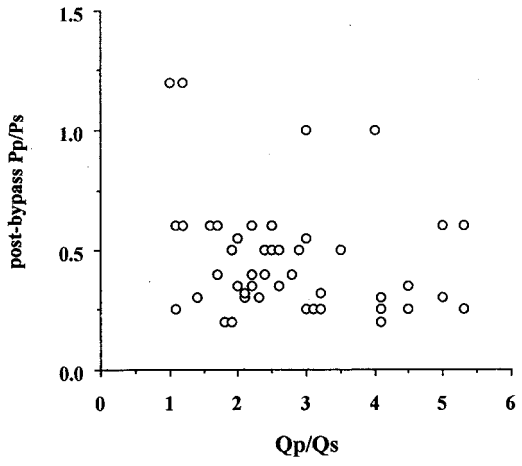

Fig. 3. Relation between preoperative pulmonary blood flow/systemic blood flow ratio ($\dot{Q}p/\dot{Q}s$) and pulmonary arterial pressure/systemic blood pressure ratio (Pp/Ps) at the time of weaning from cardiopulmonary bypass (r^2 = 0.05; P = 0.12; n = 46).

arteries and arterioles were hypertrophied (Heath-Edwards classification grade 3, IPVD score 2.1); case 25: type of intimal reaction was none, state of media of arteries and arterioles were hypertrophied (Heath-Edwards classification grade 1, IPVD score 1.0).

The histopathologic evaluation of pulmonary arterial walls in case no. 7 after death was as follows: type of intimal reaction was fibrous, state of media of arteries and arterioles were hypertrophied (Heath-Edwards classification grade 3, IPVD score 2.2), the same as preoperative findings. However, pathologic obstruction of the proximal lumen and secondary atrophy of the media of the peripheral small pulmonary arteries were observed.

Discussion

In recent years there has been an increase in surgery of infants with pulmonary hypertension, and the indication for surgery is often decided according to the results of lung biopsy, even if hemodynamics suggest the presence of Eizenmenger syndrome.[14–17]

Morphologic diagnosis of the operative indication in cases of congenital heart diseases with pulmonary hypertension is generally based on the Heath-Edwards classification. However, this classification is not adequate for the evaluation of pulmonary vascular disease in the entire pulmonary arterial system. To determine the severity of pulmonary vascular disease in the entire pulmonary arterial system, Yamaki *et al.*,[14] introduced an IPVD, which is a quantitative assessment of the plexogenic pulmonary arteriopathy. They defined the histopathologic criteria for operative indication using IPVD and reported significant positive correlations between IPVD and preoperative PVR.[14]

In this context, PVR seems to be an important measure in the preoperative assessment of patients. The results of our study suggest that preoperative PVR is a sensitive factor to the prediction of Pp/Ps at the time of weaning from CPB and is therefore very useful in predicting the development of postbypass pulmonary hypertension and in decision-making for treatment options. Preoperative high Pp/Ps has been reported to be a risk factor for postoperative pulmonary hypertension.[22] However, if Pp/Ps is high and $\dot{Q}p/\dot{Q}s$ is also high, pulmonary hypertension is secondary to excessive pulmonary perfusion, and pulmonary vascular degeneration is not yet progressive. Patients with these conditions respond to oxygen therapy and pulmonary vasodilators if pulmonary perfusion is corrected by surgery, and as a result, their Pp/Ps should decrease after surgery. In contrast, if Pp/Ps is high and $\dot{Q}p/\dot{Q}s$ is low before surgery, pulmonary vascular degeneration is already progressive, and patients may be resistant to pharmacologic treatment. Therefore, for anesthetic management, PVR seems to be more use-

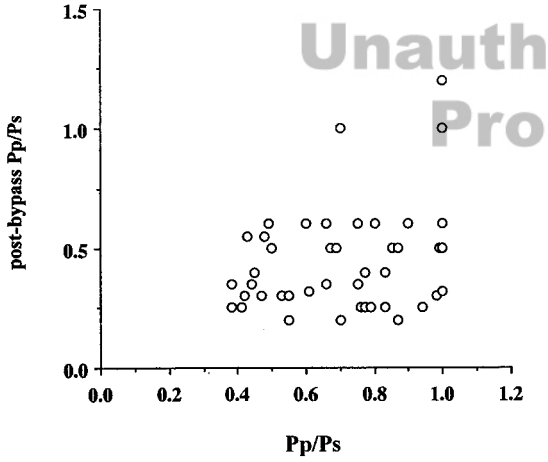

Fig. 2. Relation between preoperative pulmonary arterial pressure/systemic blood pressure ratio (Pp/Ps) and Pp/Ps at the time of weaning from cardiopulmonary bypass (r^2 = 0.13; P = 0.01; n = 46).

Table 2. Characteristics of Patients Who Developed Postbypass Pulmonary Hypertension

Case No. (Gender)	Diagnosis	Age (Month)	PVR (Wood unit m^2)	Lung Biopsy		Pp/Ps	
				H-E Class	IPVD Score	After CPB	After NO
7 (M)	cECD Down	6	15.0	Grade 3	2.1	1.2	1.2
11 (M)	ASD VSD Down	5	7.6	—	—	1.0	0.6
25 (M)	cECD Down	8	12.0	Grade 1	1.0	1.2	0.7
31 (F)	cECD Down	4	7.4	—	—	1.0	0.7

PVR = pulmonary vascular resistance; Pp/Ps = pulmonary arterial pressure/systemic blood pressure; H-E class = Heath-Edward classification; IPVD score = index of pulmonary vascular disease score; CPB = cardiopulmonary bypass; NO = nitric oxide inhalation; ASD = atrial septal defect; VSD = ventricular septal defect; Down = trisomy 21; cECD = complete endocardial cushion defects.

ful than preoperative Pp/Ps. Furthermore, Yamaki *et al.*[15] also reported that the $\dot{Q}p/\dot{Q}s$ and Pp/Ps were not useful in determining operative indications, whereas PVR proved to be the most reliable index of hemodynamics. PVR is also useful for predicting effectiveness of NO inhalation therapy in the preoperative period. In 42 patients, the postbypass pulmonary hypertension that exceeds systemic pressure was not observed in any cases in which the PVR values were less than 7 Wood units m^2, even if the preoperative Pp/Ps ratio was 1.0.

This suggests that patients with PVR values less than 7 Wood units m^2 may be treated with high-dose fentanyl,[12,13] oxygen,[6] hyperventilation,[7] and pulmonary vasodilators,[8–11] which have been reported to be effective without additional NO inhalation.

According to the literature about PVR, pulmonary hypertension persisted after surgery if PVR values were more than 6 Wood units m^2, and the prognosis was poor.[19,23,24] These articles support the results of our study, which suggest that additional NO inhalation may be useful in the anesthetic management of patients whose PVR values are greater than 7 Wood units m^2.

Of patients who had already received oxygen, hyperventilation, and pulmonary vasodilators during anesthesia, three responded to additional inhaled NO. However, one patient with a PVR value of 15 Wood units m^2 did not respond to NO inhalation, suggesting that this therapy may have limitations. In this patient (case no. 7), cardiac repair was performed 1 month after lung biopsy. It was possible that pulmonary vascular disease had progressed, because pathologic obstruction of the proximal lumen and secondary atrophy of the media of the peripheral small pulmonary arteries were observed, which were not observed in the preoperative lung biopsy. These pathologic degenerations might be one reason why this patients did not respond to NO inhalation.

In summary, preoperative PVR is a sensitive factor to the prediction of postbypass pulmonary hypertension and seems to be a measure that would predict effectiveness of inhaled NO treatment.

Limitations and Future Research Topics

In the current study, only four patients showed PVR values of more than 7 Wood units m^2 and received NO inhalation. Therefore, further studies are needed to determine the effect and usefulness of NO inhalation in patients with high PVR values and to define the criteria for inhaled NO indication using preoperative PVR values in a larger group of patients through a multiinstitutional clinical trial.

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